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JUNE 1949

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THE UNIVERSITY OF CHICAGO PRESS · CHICAGO · ILLINOIS
VOLUME 11 · · · · · NUMBER 2

THE BULLETIN OF MATHEMATICAL BIOPHYSICS

EDITED BY N. RASHEVSKY

The Bulletin is devoted to publications of research in Mathematical Biophysics, as described on the inside back cover.

THE BULLETIN is published by the University of Chicago at the University of Chicago Press, 5750 Ellis Avenue, Chicago, Illinois, quarterly, in March, June, September, December. ¶The subscription price is $4.00 per year, the price of single copies is $1.25. Orders for service of less than a full year will be charged at the single-copy rate. ¶Patrons are requested to make all remittances payable to The University of Chicago Press in postal or express money orders or bank drafts.

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BUSINESS CORRESPONDENCE should be addressed to The University of Chicago Press, Chicago, Ill.

COMMUNICATIONS FOR THE EDITOR and manuscripts should be addressed to N. Rashevsky, Editorial Office of the Bulletin of Mathematical Biophysics, 5741 Drexel Avenue, Chicago, Ill.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 11, 1949

CONTRIBUTION TO THE LINKAGE THEORY OF AUTOPOLYPLOIDS: I

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A theory of linkage of autopolyploids is developed under consideration of m loci and r alleles. The simplifying assumption of chromosome segregation, which may be considered as an approximation to the more adequate theory of chromatid segregation, is made throughout. Random mating and distinct, non-overlapping generations are assumed. Under these assumptions the problem is determined by three basic probability distributions—the distributions of genotypes and of gametes, and the segregation distribution. The segregation distribution is assumed to be the same for males and for females. The aim of the paper is to establish recurrence formulas (which allow to find the distributions of gametes and of genotypes from generation to generation, if the distribution of genotypes for an initial generation is known) and to investigate the limit behavior of these distributions as the number of generations increases indefinitely.

In the present paper (hereafter referred to as I) the problem is explained, and the three characteristic distributions are introduced for the general case of a $2s$–ploid, m loci, and r alleles. Recurrence relations are established for tetraploids, $s=2$ and $m=2$ loci, while the recurrence relations for the general case as well as the limit theorems will be given in the second part of this paper (hereafter referred to as II).

Introduction.

A linkage theory for tetraploids, $2s=4$, based on "chromosome segregation," has been presented by D. De Winton and J. B. S. Haldane (1931) for two linked factors, $m=2$, and r alleles. The case, $s=2$ and $m=3$, is also briefly considered. The same problem has been studied by F. W. Sansome (1933) under the assumption of "chromatid segregation." In a more recent paper R. A. Fisher (1947) presents a linkage theory for tetraploids and hexaploids also under the assumption of chromatid segregation. The approach is similar to that in K. Mather's (1936) study on segregation and linkage in autotetraploids.

This author has previously considered the linkage of normal, that is, diploid organisms, $s=1$, with m loci and r alleles (Geiringer, 1944; 1945). In these papers, as well as in the present paper and in the papers just quoted, random breeding and distinct, non-overlapping generations are considered. By means of an appropriate "linkage distribution" general results have been obtained. *Recurrence formulas* have been derived which enable us to compute successively the *"distribution of genotypes"* as well as the *"distribution of gametes"* from generation to generation. The main result consists of a general *limit theorem* as n, the number of generations, tends toward infinity.

On the other hand, following up an important paper by J. B. S. Haldane (1930) the author presented (Geiringer, 1948a) a mathematical theory of autopolyploids in the case of $2s$ chromosomes, one locus, and r alleles. A *"segregation distribution"* is defined which contains random chromosome segregation as considered by J. B. S. Haldane as a particular case. Again recurrence formulas are established and integrated, and the equilibrium status which presents itself, in general, as $n \rightarrow \infty$ only, is determined. A further paper which will be published in the November issue of *Genetics* deals with *chromatid segregation* of tetraploids, hexaploids and octoploids for $m = 1$. The segregation distribution which will be introduced includes, as particular cases, the segregation distribution, (s.d.), corresponding to chromosome segregation (Geiringer, 1948a) and random chromatid segregation as assumed by J. B. S. Haldane (1930), and R. A. Fisher's and K. Mather's (1943) segregation theory. Consequently, the results obtained in this paper—recurrence formulas, integration, and limit theorems—apply to all these situations.

In the present paper, returning to the assumption of chromosome segregation, we consider the general problem *of* m *loci for a 2s-ploid with* r *alleles*. An adequate setup must include as particular cases the problems of diploids of m loci (Geiringer, 1944), $s=1$, general m, and of a $2s$-ploid and one locus (Geiringer, 1948a), $m=1$, general s. Moreover the case of a $2s_1$-ploid with m_1 loci, ($s_1 \leqq s$, $m_1 \leqq m$), must appear as a "marginal" case of the more general case. More explicitly, if by an appropriate marginal summation, applied to any of our distributions, for example, to the distribution of gametes or to the s.d., we reduce the m to m_1 and the s to s_1, the marginal distribution so obtained must be a distribution of gametes or a s.d. for a $2s_1$-ploid with m_1 loci.

The theory is based on the definition of a general s.d. which is given in section 2 for $m=s=2$, and in section 4 for general m and s. This s.d., which, of course fulfills the above requirements, contains as particular cases random chromosome segregation, as considered briefly by J. B. S. Haldane (1930) and De Winton and Haldane's segregation theory(see section 3 of the present paper). The main result is a surprisingly simple and general *limit theorem* which also completely settles the question of the existence of an equilibrium status (sections 3 and 5 of II). It is based on *recurrence relations* (section 1 of II) between the distributions of gametes in two successive generations. (From the distribution of gametes we easily deduce the distribution of genotypes, if random mating is assumed.) The recurrence formulas form a system of quadratic difference equations whose constant coefficients are the values of our s.d.

As has been said, the theory applies to chromosome segregation only. It seemed necessary to present the theory under this simplifying assumption before dealing with the very considerable additional complications of chromatid segregation, considered, so far, by the author for $m=1$ only (Geiringer, 1949). Chromosome segregation forms an approximation to the more adequate assumption of chromatid segregation. It is also assumed that the same s.d. applies to males and to females. The desirable generalization to different s.d.'s for the two sexes may not be too difficult (see Geiringer, 1948b where this is carried out for $s=1$ and general m). It is however not attempted in the present paper. The ideas developed in this paper may seem too abstract and formal to the majority of geneticists. The difficulties of some problems of modern heredity are quite considerable and seem to call for a mathematical approach. Since in science there is a mutual interaction between observation and theory, it is hoped that such an approach may, sooner or later, prove useful to theoretical genetics, although it emphasizes only one side of a complex problem.

Let us finally point out that the linkage theory presented here forms the framework of a theory rather than a specific theory, inasmuch as no particular assumptions are advanced regarding the parameters which enter into the definition of the s.d. The theory is to be completed by biologically adequate "models" of a s.d. such as in R. A. Fisher and K. Mather (1943), or in H. Geiringer (1944). In this sense Haldane's linkage theory constitutes a particularly simple model. The results of the present paper apply to a great variety of models. Thus they describe, e.g., the limit behavior of the basic genetic distributions for De Winton and Haldane's linkage theory.

1. *Notations and Definitions.*

As in the introduction, let $2s$ denote the number of chromosomes in the zygote; m, the number of loci; r, that of alleles. We assume that the concepts for $m=1$ are more or less known (see Haldane, 1930; Fisher and Mather, 1943; and Geiringer, 1948a). We start with the consideration of a tetraploid with two loci and two alleles, $m=s=r=2$. Our first task is to *enumerate* the possible gametic and zygotic types and to introduce a suitable *notation.* If we attempt this we see immediately that there are various possibilities of differentiation. We shall mention four of them, beginning with the consideration of zygotes.

1) One may assume that a zygotic type is satisfactorily characterized if the *four values* are stated which correspond to *each locus,* such as $(AAAaBBBB)$ or (A^3aB^4). This is, in fact, sufficient if, as in J. B. S. Haldane (1930), no linkage is considered.

2) De Winton and Haldane, in their paper on linkage, show in their notation the *four chromosomes* which constitute a zygotic type, denoting such a type, for example, by (AB,AB,Ab,ab) where the chromosomes are separated by commas, and where the order of the chromosomes plays no role. In this conception (AB,Ab,Ab,aB) and (AB,AB,Ab,ab) represent different types, while in notation 1) they both appear as $(A^3aB^2b^2)$.

3) We may choose to show the *maternal and paternal heritage* of the zygote in our notation. The reason for this will be discussed at the end of this section. This may be done without indicating the four chromosomes. We may simply write the "maternal values" before a semicolon and the paternal ones after, for example, $(A^2b^2;AaB^2)$. If we denote the whole maternal heritage of an organism by x, the whole paternal one by y, we shall assume that $(x;y) = (y;x)$.

4) Finally, parental *heritage as well as chromosomes* may be shown. A type may then be denoted by $(AB,Ab;AB,aB)$ and we assume, as before, that $(x;y) = (y;x)$ and that the order of the two chromosomes before or after the semicolon plays no role.

Let us count the number of different types under these various assumptions. Without any "symmetry relations" there would be $2^8=256$ different types. According to the four assumptions this number reduces considerably. There are under the

first assumption	$n_1=25$	different	types;
second "	$n_2=35$	"	" ;
third "	$n_3=45$	"	" ;
fourth "	$n_4=55$	"	" .

These numbers are easily understood. We find all possible types in the first case by symbolical multiplication of $(A^4 + 4A^3a + 6A^2a^2 + 4Aa^3 + a^4)$ by $(B^4 + \cdots + b^4)$. Hence there are 25 different types. The coefficients, for example, $24(A^3aB^2b^2)$, indicate how many of the original 256 types are lumped together. In the second case we shall denote, for the moment, the four chromosomes by u, v, w, and s.

The possible types correspond to the terms appearing in the expansion of $(u+v+w+s)^4$, hence comprise 35 types, and the coefficient of each type appears also in this polynomial formula. In a similar way we may establish the number of types for the third and fourth cases.

The enumeration of the *gametic types* is simpler. Here no analogue to notations 3) or 4) exists. We merely may or may not show the two chromosomes in a gamete.

1) If they are not shown, we assume that the gamete is completely specified by stating the four values, such as $(AABB) = (A^2B^2)$. There are then obviously nine different types.

2) If chromosomes are shown then the types (AB,ab) and (Ab,aB) are distinct and there are ten types.

Now consider *a 2*s*-ploid with* m *loci and* r *alleles.* A zygotic type is then denoted, e.g., under the fourth assumption:

$$\begin{gathered}(x_1^{(1)} \cdots\cdot x_m^{(1)}, \cdots\cdot, x_1^{(s)} \cdots\cdot x_m^{(s)};\\ y_1^{(1)} \cdots\cdot y_m^{(1)}, \cdots\cdot, y_1^{(s)} \cdots\cdot y_m^{(s)}).\end{gathered}$$

Here $x_i^{(j)}$ is the maternal value corresponding to the ith locus in the jth chromosome, and $y_i^{(j)}$ means the same for paternal values, $(i = 1, \cdots\cdot m, j = 1, \cdots\cdot s)$. There are $2sm$ places, each to be filled with one of r numbers. Consequently there would be $N' = r^{2sm}$ types if there were no symmetry relations at all. Corresponding to the four ways of differentiation we get the following numbers without difficulty:

1) $$n_1 = \left[\binom{r+2s-1}{r-1}\right]^m = \left[\binom{r+2s-1}{2s}\right]^m.$$

This reduces for $s=1$ and any m and r to $\left[\frac{r(r+1)}{2}\right]^m$ which was denoted by N_2 in H. Geiringer (1944); while for $m=1$, and any s and r, we find the number $N_2' = \binom{r+2s-1}{2s}$, as in H. Geiringer (1948a).

2) This leads to

$$n_2 = \binom{r^m + 2s - 1}{2s},$$

which for $s=1$ gives $N_1 = \frac{1}{2} r^m (r^m + 1)$ as in H. Geiringer (1944); while for $m=1$ we again find N_2'.

3) Here

$$n_3 = \tfrac{1}{2}\left[\binom{s+r-1}{r-1}\right]^m \cdot \left\{\left[\binom{s+r-1}{r-1}\right]^m + 1\right\} .$$

For $s = 1$ we again have N_1 and for $m = 1$, with $R = \binom{s+r-1}{s}$, we have $N_1' = \frac{1}{2} R(R+1)$ as in H. Geiringer (1948a).

4) Finally

$$n_4 = \tfrac{1}{2}\binom{r^m + s - 1}{s} \cdot \left[\binom{r^m + s - 1}{s} + 1\right],$$

which for $m = 1$, any s and r, reduces to N_1' and for $s = 1$, any m and r, to N_1.

If r_i denotes the number of possible alleles at the ith locus, $(i = 1, \cdots m)$, the corresponding expressions are:

1 $\prod_{i}^{1 \ldots m} \binom{r_i + 2s - 1}{r_i - 1}$;

2) $\binom{r_1 r_2 \cdots r_m + 2s - 1}{2s}$;

3 $\prod_{i}^{1 \ldots m} \binom{s + r_i - 1}{r_i - 1}$ takes the place of $\left[\binom{s+r-1}{r-1}\right]^m$;

4) $r_1 r_2 \cdots r_m$ takes the place of r^m.

We may however assume without loss of generality that there are r possible alleles at each locus. In fact, we shall denote by r the greatest of the m numbers, r_i. To assume this same r at each locus amounts merely to the assumption that the genetic probabilities of certain types within the distribution of genotypes are zero. It is an unnecessary complication to consider, as some authors do, all possible combinations connected with different r_i at the ith locus.

The differentiation between the various chromosomes as in 2) and 4) exists neither for $s = 1$, general m, nor for $m = 1$, general s. In these situations only assumptions 1) and 3) come under consideration, and assumption 3) was considered by H. Geiringer (1944 and 1948a); (see end of this section).

Next let us introduce the probability *distribution of gametes* (d.ga) and the probability *distribution of zygotes* (d.z), or of genotypes. We consider again the case $m = s = r = 2$, the general distributions (which are completely analogous to those for $m=s=r=2$) being needed in section 1 of II only. We shall denote by

$$\binom{2}{z_1}\cdot\binom{2}{z_2}p^{(n)}(A^{z_1}a^{2-z_1}B^{z_2}b^{2-z_2}), \qquad \begin{pmatrix} z_1=0,1,2 \\ z_2=0,1,2 \end{pmatrix};$$

the probability of a gamete of type $(A^{z_1}a^{2-z_1}B^{z_2}b^{2-z_2})$ in the nth generation, where

$$\begin{gathered}\sum_{z_1}^{0\ldots2}\sum_{z_2}^{0\ldots2}\binom{2}{z_1}\cdot\binom{2}{z_2}p^{(n)}(A^{z_1}a^{2-z_1}B^{z_2}b^{2-z_2})=1, \\ (n=0,1,\cdots),\end{gathered} \tag{1}$$

or, more explicitly,

$$\begin{aligned}&p^{(n)}(A^2B^2)+2p^{(n)}(A^2Bb)+p^{(n)}(A^2b^2)\\ &+2p^{(n)}(AaB^2)+4p^{(n)}(AaBb)+\cdots+p^{(n)}(a^2b^2)=1.\end{aligned}$$

We shall also denote, according to assumption 3), by

$$\binom{2}{x_1}\binom{2}{x_2}\binom{2}{y_1}\binom{2}{y_2}w^{(n)}(A^{x_1}a^{2-x_1}B^{x_2}b^{2-x_2};A^{y_1}a^{2-y_1}B^{y_2}b^{2-y_2})$$

the probability in the nth generation of a zygote of the type indicated within the parenthesis. Here

$$\begin{gathered}\sum_{x_1}^{0\ldots2}\sum_{x_2}^{0\ldots2}\sum_{y_1}^{0\ldots2}\sum_{y_2}^{0\ldots2}\binom{2}{x_1}\cdot\binom{2}{x_2}\cdot\binom{2}{y_1}\cdot\binom{2}{y_2}\\ \cdot w^{(n)}(A^{x_1}a^{2-x_1}B^{x_2}b^{2-x_2};A^{y_1}a^{2-y_1}B^{y_2}b^{2-y_2})=1, \quad (n=0,1,\cdots).\end{gathered} \tag{2}$$

As before, we shall sometimes denote the whole expression

$$A^{x_1}a^{2-x_1}B^{x_2}b^{2-x_2}$$

which in w stands before the semicolon, by x, and similarly we shall denote by y the analogous expression after the semicolon. The fact that we consider $(x;y)$ and $(y;x)$ as identical types corresponds to assuming

$$w^{(n)}(x;y)=w^{(n)}(y;x), \qquad (n=0,1,\cdots). \tag{3}$$

Under random breeding a new individual of the $(n+1)$st generation is formed by the random fusion of two gametes of the nth generation. This is expressed in the basic formula,

$$w^{(n+1)}(x;y)=p^{(n)}(x)\,p^{(n)}(y); \qquad (n=0,1,\cdots). \tag{4}$$

Let us conclude this section by commenting upon notation 3) adopted by us, which amounts to introducing a differentiation between the paternal and maternal heritage of an organism. This differentiation is assumed merely with respect to the formation of gametes. In the simplest case, $s=1$, $m=2$, we know that *there is* a difference between an organism $(AB;ab)$ and $(Ab;aB)$ with respect to the formation of gametes, i.e., with respect to linkage. The former will transmit (Ab) or (aB) with probability "c" (recombination value); while the latter will transmit them with probability $(1-c)$. Thus if linkage is considered there are not nine but ten types for $s=1$, $m=r=2$. For larger "m" this differentiation seems unavoidable in connection with linkage (see Geiringer, 1944). It seems to the author that, if $s > 1$, the theoretical consideration of linkage calls even more for this differentiation.[†]

This differentiation is indispensable in order to *find* and to understand certain regularities whose proof forms the subject of the author's genetical investigations. It is, in fact, possible to show that in rather general situations certain *biological laws* hold which are of a clear, simple and uniform structure. They are concerned with: 1) *recurrence formulas* which show how the basic distributions of gametes and of zygotes in the $(n+1)$st generation are determined by the distributions in the nth generation; 2) the characterization of a possible *equilibrium status,* a problem that includes the study of the limit behavior of the distributions as n tends toward infinity. For these purposes, which are of a biological nature, the more general notation 3)—far from introducing an unnecessary complication—is of decisive importance. As a very simple illustration of this consider equation (4). If we do not show paternal and maternal heritage we would, for example, denote by

$$\binom{4}{1}\cdot\binom{4}{2} v^{(n)}(A^3aB^2b^2)$$

the probability of a zygote of type $(A^3aB^2b^2)$ and we would have

$$\begin{aligned} 24v^{(n)}(A^3aB^2b^2) = 2[&2w^{(n)}(A^2B^2; Aab^2) \\ &+ 8w^{(n)}(A^2Bb;AaBb) + 2w^{(n)}(A^2b^2;Aab^2)], \end{aligned}$$

and therefore, corresponding to (4),

$$\begin{aligned} 6v^{(n+1)}(A^3aB^2b^2) = {}& p^{(n)}(A^2B^2)\, p^{(n)}(AaB^2) \\ &+ 4p^{(n)}(A^2Bb)\, p^{(n)}(AaBb) + p^{(n)}(A^2b^2)\, p^{(n)}(AaB^2), \end{aligned}$$

instead of the clear formula (4), thus

[†] In Haldane's linkage theory (section 3 of the present paper) polyploid linkage is reduced to the consideration of diploid linkage.

$$w^{(n+1)}(A^2B^2;Aab^2)=p^{(n)}(A^2B^2)\,p^{(n)}(Aab^2),$$
$$w^{(n+1)}(A^2Bb;AaBb)=p^{(n)}(A^2Bb)\,p^{(n)}(AaBb),\text{ etc.}$$

For greater values of m and s these complications would become still more marked.

Another remark regarding the differentiation contained in notation 3) is the following: Our final recurrence formula (section 1 of II) *is for gametes,* which means we compute $p^{(n+1)}$ from $p^{(n)}$, hence notation 3) in no way enters into this final result. A similar remark applies to our limit theorem. On the other hand, if we want a limit result or a recurrent computation for the d.z. this follows immediately from the respective result for the d.ga. by means of (4). Finally, it is extremely easy to eliminate this differentiation 3) after it has served its purpose if we are concerned with a problem in which it seems irrelevant. We have merely to omit the semicolon and lump together the values separated by it.

2. *The Segregation Distribution for* m=s=2.

Let us again start with the consideration of a tetraploid with two factors, the case mainly considered in the literature of our problem. The fundamental definition is that of the s.d. Our definition will again be based on assumption 3) where we show the parental heritage but not necessarily the various chromosomes. The number of alleles may be arbitrary. Consider a zygote of type $(a_1a_2b_1b_2;\, a_3a_4b_3b_4)$ where a_i denotes an allele with respect to the first factor, b_i one with respect to the second factor. We introduce

$$\left[\binom{2}{\varepsilon_1}\right]^2\left[\binom{2}{\varepsilon_2}\right]^2\lambda(\varepsilon_1\,\varepsilon_2);\qquad(\varepsilon_1=0;1,2;\varepsilon_2=0,1,2),$$

the probability that ε_1 *maternal* a*-values and* ε_2 *maternal* b*-values be transmitted,* (and, consequently, $2-\varepsilon_1$ paternal a-values and $2-\varepsilon_2$ paternal b-values). Thus $\lambda(00)$ is the probability that no maternal value will be transmitted, and, consequently, the four paternal values, a_3, a_4, b_3, b_4, will be transmitted. In the same way $4\lambda(10)$ is the probability that either $(a_1a_3b_3b_4)$, $(a_1a_4b_3b_4)$, $(a_2a_3b_3b_4)$, or $(a_2a_4b_3b_4)$ will be transmitted and we assume that these four probabilities are equal. Moreover, as in previous papers, we have to assume "symmetry" with respect to paternal and maternal heritage. This amounts to putting

$$\lambda(\varepsilon_1\,\varepsilon_2)=\lambda(2-\varepsilon_1,2-\varepsilon_2).\tag{5}$$

Hence there are five parameters with sum one. In fact, because of (5), the equation

$$\begin{aligned}&\lambda(00)+4\lambda(10)+4\lambda(01)+16\lambda(11)+\lambda(02)\\&+\lambda(20)+4\lambda(12)+4\lambda(21)+\lambda(22)=1\end{aligned}\qquad(6)$$

reduces to

$$2\lambda(00)+8\lambda(10)+8\lambda(01)+16\lambda(11)+2\lambda(02)=1.\qquad(7)$$

It will be convenient to introduce also

$$l(\varepsilon_1\,\varepsilon_2)=\binom{2}{\varepsilon_1}\binom{2}{\varepsilon_2}\lambda(\varepsilon_1\,\varepsilon_2),\qquad(8)$$

the probability that a fixed set of ε_1 maternal a-values and a fixed set of ε_2 maternal b-values will be transmitted. If, for example, the fixed set consists of a_1 and b_1,

$$\begin{aligned}l(11)=\text{Prob}\,[(a_1b_1a_3b_3)+(a_1b_1a_3b_4)+(a_1b_1a_4b_3)\\+(a_1b_1a_4b_4)]=4\lambda(11),\end{aligned}$$

where "Prob [····]" means "probability to transmit the expression in brackets."

We then have

$$\begin{aligned}\sum_{\varepsilon_1}^{0\ldots.2}\sum_{\varepsilon_2}^{0\ldots.2}\left[\binom{2}{\varepsilon_1}\right]^2\left[\binom{2}{\varepsilon_2}\right]^2\lambda(\varepsilon_1\,\varepsilon_2)=\sum_{\varepsilon_1}^{0\ldots.2}\sum_{\varepsilon_2}^{0\ldots.2}\binom{2}{\varepsilon_1}\binom{2}{\varepsilon_2}l(\varepsilon_1\,\varepsilon_2)\\=1.\end{aligned}\qquad(9)$$

Let us now introduce certain *"marginal distributions"* of our s.d. With the above notation for "Prob [····]" where we agree that the order of the four values within the parentheses is irrelevant we consider

$$\begin{aligned}\text{Prob}\,[(a_1a_2b_1b_2)+(a_1a_2b_1b_3)+(a_1a_2b_1b_4)+(a_1a_2b_2b_3)\\+(a_1a_2b_2b_4)+(a_1a_2b_3b_4)].\end{aligned}$$

This is obviously the probability that, no matter what happens to the b-factors, the maternal a-factors, a_1 and a_2, are transmitted. Hence it is a marginal probability and equal to

$$\lambda(22)+4\lambda(21)+\lambda(20)=l(22)+2l(11)+l(20)=l_1(2).$$

In general $\binom{2}{\varepsilon}l_i(\varepsilon)$ is the probability that, as far as the ith factor is concerned, ε maternal values are transmitted. Thus for $\varepsilon=0,1,2$ we have

$$l_1(\varepsilon) = l(\varepsilon, 0) + 2l(\varepsilon, 1) + l(\varepsilon, 2), \tag{10}$$

and

$$l_2(\varepsilon) = l(0, \varepsilon) + 2l(1, \varepsilon) + l(2, \varepsilon), \tag{11}$$

with the relations

$$l_i(0) = l_i(2), \quad l_i(0) + 2l_i(1) + l_i(2) = 1; \quad (i = 1, 2). \tag{12}$$

We note that each of these two marginal distributions has the same properties as the s.d. for $m=1$ in H. Geiringer (1948a).

On the other hand consider the following marginal probability for the event that a_1 and b_1 are transmitted no matter which are the other transmitted values:

$$\begin{aligned}\text{Prob}\,[&(a_1b_1a_2b_2) + (a_1b_1a_2b_3) + (a_1b_1a_2b_4) + (a_1b_1a_3b_2)\\ &+ (a_1b_1a_3b_3) + (a_1b_1a_3b_4) + (a_1b_1a_4b_2)\\ &+ (a_1b_1a_4b_3) + (a_1b_1a_4b_4)]\,.\end{aligned}$$

We denote this probability by $l^{(1)(1)}(11)$. This notation indicates, with respect to the superscripts, that the "*s*" of each of the two loci has been reduced by *one*. If there is no possibility of a misunderstanding we may also denote this distribution by $l_{12}(\varepsilon_1\ \varepsilon_2)$, $(\varepsilon_i = 0, 1)$, since it is a linkage distribution with all the properties of the linkage distribution for diploids as in H. Geiringer (1944). We then have

$$\begin{aligned}l_{12}(11) &= \lambda(22) + 2\lambda(21) + 2\lambda(12) + 4\lambda(11)\\ &= l(11) + l(21) + l(12) + l(22);\\ l_{12}(10) &= l(10) + l(20) + l(11) + l(21);\\ l_{12}(01) &= l(01) + l(11) + l(02) + l(12);\\ l_{12}(00) &= l(00) + l(10) + l(01) + l(11);\end{aligned} \tag{13}$$

with the symmetry relations following from (5)

$$l_{12}(00) = l_{12}(11), \quad l_{12}(01) = l_{12}(10). \tag{14}$$

From (9) we conclude

$$\begin{aligned}l_{12}(00) &+ l_{12}(01) + l_{12}(10) + l_{12}(11)\\ &= 2l_{12}(00) + 2l_{12}(01) = 1\,.\end{aligned} \tag{15}$$

From this linkage distribution we derive, in particular, the recombination probability (r.p.)

$$c_{12} = l_{12}(10) + l_{12}(01) = 2l_{12}(10) = 1 - 2l_{12}(00).$$

We have thus introduced a s.d. for $m=s=2$, which contains the five parameters $l(00)$, $l(10)$, $l(01)$, $l(20)$, and $l(11)$ which, because of (9), reduce to four. The following relations hold for these parameters

$$l(00) + 2l(01) + l(02) = l_1(0)\,; \tag{16}$$

$$l(00) + 2l(10) + l(20) = l_2(0)\,; \tag{17}$$

$$l(00) + l(10) + l(01) + l(11) = l_{12}(00)\,; \tag{18}$$

where $l_i(0)$ is the parameter of the s.d. for $s=2$ with respect to the ith character and $c_{12} = 1 - 2l_{12}(00)$ is the r.p. between the two loci as $s=1$. If we know $l_1(0)$, $l_2(0)$, and c_{12} from observations on monofactorial tetraploids or bifactorial diploids of the same plant, there are four relations between the five parameters.

Let us finally characterize the important particular case of "independence" for our s.d. We call a s.d., $l(\varepsilon_1\, \varepsilon_2)$, "independent" if

$$l(\varepsilon_1\, \varepsilon_2) = l_1(\varepsilon_1)\, l_2(\varepsilon_2), \tag{19}$$

where, as we easily see, $l_i(\varepsilon_i)$ are the marginal distributions introduced in (10) and (11). *In this case the matrix*

$$\{l(\varepsilon_1\, \varepsilon_2)\}\,, \quad (\varepsilon_1 = 0\,,1\,,2\,;\, \varepsilon_2 = 0\,,1\,,2), \tag{20}$$

is of rank one, and vice versa, as can be seen without difficulty by means of (5). It also follows that in this case

$$l_{12}(00) = l_{12}(10) = l_{12}(01) = l_{12}(11) = \tfrac{1}{4}\,, \quad c_{12} = \tfrac{1}{2}\,; \tag{21}$$

hence there is no linkage, in the sense of diploid linkage. A particular case of independence presents itself if all

$$\begin{gathered} \lambda(\varepsilon_1\, \varepsilon_2) = \frac{1}{36}, \quad \varepsilon_1 = 0, 1, 2; \quad \varepsilon_2 = 0, 1, 2 \\ l_1(0) = l_2(0) = \frac{1}{6}, \quad 2l_1(1) = 2l_2(1) = \frac{4}{6}. \end{gathered} \tag{22}$$

Hence, *if the s.d. of the tetraploid is independent, and, in particular, if it is uniform, i.e., if each* $\lambda(\varepsilon_1\, \varepsilon_2) = 1/36$, *there is no diploid linkage. If there is no diploid linkage the s.d. is independent.*

The definition of our s.d., as given in this section, is again based on the differentiation 3). We shall comment upon this after the role of the s.d. in our recurrence formulas (section 1 of II) has been established. Let us finally point out that under the assumption of chromosome segregation a s.d. for tetraploids with two loci cannot account for more than $\binom{4}{2} \cdot \binom{4}{2} = 36$ gametic outputs. If chromatid segregation is considered, there are $\binom{8}{2} \cdot \binom{8}{2} = 28^2$ possible gametic outputs.† Our aim in this paper is to carry out the consequences of a general chromosome segregation theory.

3. *De Winton and Haldane's Linkage Theory for Tetraploids.*

The linkage theory proposed by De Winton and Haldane with respect to the tetraploid primula, $m=s=2$, is as follows. A zygote consists of four chromosomes which are denoted by A_1B_1, A_2B_2, A_3B_3, A_4B_4 or by K_1, K_2, K_3, K_4. Starting from observations the authors arrive at a linkage theory by the following considerations. In one third of all cases K_1 will pair with K_2 and, on the other hand, K_3 with K_4. In one third of the cases K_1 pairs with K_3 and K_2 with K_4, and in one third of the cases K_1 pairs with K_4 and K_2 with K_3. Next it is assumed that for each such pairing ordinary *diploid linkage* prevails. That amounts to the following:

As K_1 pairs with K_2,

A_1B_1 will be transmitted with probability $\frac{q}{2}=\frac{1-p}{2}=\frac{1-c_{12}}{2}$;

A_2B_1 ” ” ” ” ” $\frac{p}{2}=\frac{c_{12}}{2}$;

A_1B_2 ” ” ” ” ” $\frac{p}{2}$;

A_2B_2 ” ” ” ” ” $\frac{q}{2}$;

and as K_3 pairs with K_4,

A_3B_3 will be transmitted with probability $q/2$;
A_4B_3 ” ” ” ” ” $p/2$;
A_3B_4 ” ” ” ” ” $p/2$;
A_4B_4 ” ” ” ” ” $q/2$.

Next, assuming *independent combination of probabilities;* it follows that:

$A_1B_1A_3B_3$ will be transmitted with probability $\frac{1}{3}\frac{q^2}{4}$;

---

†Among these 28 · 28 gametic outputs there are many which cannot be obtained under chromosome segregation. There are 100 different gametes possible. Besides the 36 which appear under chromosome segregation, there are 16 of type $A_i^2B_j^2$ $(i=1,\cdots 4;\ j=1,\cdots 4)$, and 48 of types $A_i^2B_jB_k$, or $B_i^2A_jA_k$ where $j\neq k$.

$A_1B_1A_3B_4$ " " " " " $\frac{1}{3}\frac{pq}{2}$;

$A_1B_1A_4B_3$ " " " " " $\frac{1}{3}\frac{pq}{2}$;

. . . .

$A_2B_2A_4B_4$ " " " " " $\frac{1}{3}\frac{q^2}{4}$.

Thus, in an obvious notation we see that if

$$1) \qquad (A_1B_1, A_2B_2) \times (A_3B_3, A_4B_4),$$

the four combinations

$$\begin{gathered} A_1B_1A_3B_3 \\ A_1B_1A_4B_4 \\ A_2B_2A_3B_3 \\ A_2B_2A_4B_4 \end{gathered}$$

are transmitted each with probability $\frac{q^2}{12}$, while

$$\begin{gathered} A_1B_2A_3B_4 \\ A_1B_2A_4B_3 \\ A_2B_1A_3B_4 \\ A_2B_1A_4B_3 \end{gathered}$$

are transmitted each with probability $\frac{p^2}{12}$, and the eight combinations

$$\begin{matrix} A_1B_1A_3B_4 & \qquad & A_1B_2A_3B_3 \\ A_1B_1A_4B_3 & & A_1B_2A_4B_4 \\ A_2B_2A_3B_4 & & A_2B_1A_3B_3 \\ A_2B_2A_4B_3 & & A_2B_1A_4B_4 \end{matrix}$$

are each transmitted with probability $pq/12$. Next if

$$2) \qquad (A_1B_1, A_3B_3) \times (A_2B_2, A_4B_4),$$

the four combinations

$$\begin{gathered} A_1B_1A_2B_2 \\ A_1B_1A_4B_4 \\ A_3B_3A_2B_2 \\ A_3B_3A_4B_4 \end{gathered}$$

are transmitted each with probability $\frac{q^2}{4}$, while

$$A_1B_3A_2B_4$$
$$A_1B_3A_4B_2$$
$$A_3B_1A_2B_4$$
$$A_3B_1A_4B_2$$

are transmitted each with probability $\frac{p^2}{4}$, and

$$\begin{array}{llll} A_1B_1A_2B_4\,, & A_1B_1A_4B_4\,, & A_3B_3A_2B_4\,, & A_3B_3A_2B_2 \\ A_1B_3A_2B_2\,, & A_1B_3A_4B_4\,, & A_3B_1A_2B_2\,, & A_3B_1A_4B_4 \end{array}$$

all with probability $pq/12$. The results of the pairing

3) $$(A_1B_1\,, A_4B_4) \times (A_2B_2\,, A_3B_3)$$

can be worked out in a similar way.

In order to summarize these 48 results we briefly introduce, just for this purpose, the following probability distribution. Denote by l_{22} each of the six probabilities that the four transmitted values come from only *two* chromosomes. Thus, e.g., l_{22} is the probability for transmitting $A_1B_1A_2B_2$. In the same way $6l_{1111}$ denotes the probability that the four transmitted values are from *four* different chromosomes, e.g., $A_1B_2A_3B_4$ and $24l_{211}$ is the probability that three different chromosomes take part, e.g., $A_1B_1A_2B_3$. We then have

$$6l_{22} + 6l_{1111} + 24l_{211} = 1\,. \tag{23}$$

De Winton and Haldane's theory then amounts to assuming that

$$l_{22} = \frac{q^2}{6}, \quad l_{1111} = \frac{p^2}{6}, \quad l_{211} = \frac{pq}{12}, \tag{24}$$

in accordance with (23).

Let us indicate a few further consequences of this theory. Our postulate regarding marginal summations (see the introduction) is satisfied. We get, in fact,

$$\begin{gathered} l_1(0) = l_2(0) = \frac{1}{6}, \quad 2l_1(1) = 2l_2(1) = \frac{4}{6}; \\ l_{12}(00) = l_{12}(11) = \frac{p}{2}, \quad l_{12}(10) = l_{12}(01) = \frac{q}{2}. \end{gathered} \tag{25}$$

Next, it is easy to compute our values $l(00)$, $l(10)$, $\cdots$ $l(02)$ (section 2) for Haldane's theory. We find: $l(00) = l(22) = q^2/6$,

$2l(01) = 2l(10) = 2l(21) = 2l(12) = pq/3, 4l(11) = \frac{2}{3}(p^2 + pq + q^2)$,
$l(20) = l(02) = p^2/6$.

The authors point out that in this theory it is possible to distinguish "between 50% crossing over and the absence of linkage." That means, in our notation, that for $p=q=1/2$ we do not obtain 36 equal segregation probabilities as we would for *random* chromosome segregation. In fact, if $p=q=1/2$ we obtain

$$l_{22} = l_{1111} = \frac{1}{24}, \quad l_{211} = \frac{1}{48}. \qquad (26)$$

This is a consequence of the assumption, suggested by the material observed, that pairing occurs in the above indicated manner. Moreover, a uniform s.d., or random chromosome segregation, can never be obtained in this theory no matter how we choose the parameters. In fact, putting

$$l_{22} = l_{211} = l_{1111} = \frac{1}{36}$$

leads to contradiction with (24). (If $q^2/6 = p^2/6$ then $p=q$ follows and $l_{211} = \frac{pq}{12} = \frac{p^2}{12} \neq \frac{p^2}{6}$.) It seems that a theory in which a uniform s.d. is impossible cannot be considered as a *general* linkage theory for tetraploids. In this theory, which has been designed in order to explain a particular set of data from observations, the problem of tetraploid linkage is reduced to diploid linkage.

If the theory is generalized to $s=2$, $m=3$ it can be seen that of the 216 possible gametes, certain types do not appear. Hence this theory may apply to a situation in which certain classes of gametes are absent.

4. *The General Segregation Distribution.*

We now consider a $2s$-ploid with m loci each determined by one of r alleles. In the formation of a new individual corresponding to each locus, a set of s values is transmitted. We shall define a general chromosome segregation distribution. Denote by

$$\left[\binom{s}{\varepsilon_1}\right]^2 \cdots \left[\binom{s}{\varepsilon_m}\right]^2 \lambda(\varepsilon_1 \cdots \varepsilon_m); \qquad (\varepsilon_i = 0, 1, \cdots s), \quad (27)$$

the probability that the transmitted set of s *values which corresponds to the* ith *locus contains* ε_i *maternal values* (and, consequently, $s - \varepsilon_i$

paternal ones) where $\varepsilon_i = 0, 1, \cdots s; i = 1, 2, \cdots m$. Each single $\lambda(\varepsilon_1\ \varepsilon_2 \cdots \varepsilon_m)$ is the probability for a *specified* set of maternal and of paternal values and

$$\binom{s}{\varepsilon_1} \cdots \binom{s}{\varepsilon_m} \lambda(\varepsilon_1 \cdots \varepsilon_m) = l(\varepsilon_1 \cdots \varepsilon_m) \tag{28}$$

is the probability for a specified set of maternal values (see section 2). We then have

$$\begin{aligned}&\sum_{\varepsilon_1}^{0\ldots s} \cdots \sum_{\varepsilon_m}^{0\ldots s} \left[\binom{s}{\varepsilon_1}\right]^2 \cdots \left[\binom{s}{\varepsilon_m}\right]^2 \lambda(\varepsilon_1 \cdots \varepsilon_m)\\ &= \sum_{\varepsilon_1}^{0\ldots s} \cdots \sum_{\varepsilon_m}^{0\ldots s} \binom{s}{\varepsilon_1} \cdots \binom{s}{\varepsilon_m} l(\varepsilon_1 \cdots \varepsilon_m) = 1.\end{aligned} \tag{29}$$

As in section 2 of this paper and in earlier papers (Geiringer, 1944; 1948a) we have to assume a symmetry relation

$$l(\varepsilon_1 \cdots \varepsilon_m) = l(s - \varepsilon_1, \cdots, s - \varepsilon_m). \tag{30}$$

We see that for $s=1$ and general "m" (27) reduces to a linkage distribution (l.d.) as defined and used in H. Geiringer (1944), and for $m=1$ and general s to the s.d. defined and used in H. Geiringer (1948a). The s.d. (27) is a discontinuous (arithmetical) m-variate distribution, each variable equal to $0, 1, \cdots$ or s, and for which the relations (29) and (30) hold.

We next introduce the *marginal distributions* of this s.d. We shall show that by an appropriate "marginal summation" we are able to reduce the "s", the "m", or both. *From* $l(\varepsilon_1 \cdots \varepsilon_m)$ *we derive by a* $(\nu_1 + \cdots + \nu_m)$*-tuple summation,* $(0 \leqq \nu_i \leqq s)$, *the marginal distribution,*

$$\begin{aligned}&l^{(\nu_1)\ldots(\nu_m)}(\varepsilon_1 \cdots \varepsilon_m)\\ &= \sum_{\eta_1}^{0\ldots\nu_1} \cdots \sum_{\eta_m}^{0\ldots\nu_m} l(\varepsilon_1 + \eta_1, \cdots \varepsilon_m + \eta_m) \cdot \binom{\nu_1}{\eta_1} \cdots \binom{\nu_m}{\eta_m},\end{aligned} \tag{31}$$

where

$$\varepsilon_i = 0, 1, \cdots (s - \nu_i), \qquad (i = 1, \cdots m). \tag{32}$$

In a symbolical way which is both useful and suggestive, the definition (31) may be written

$$l^{(\nu_1)\ldots(\nu_m)}(\varepsilon_1 \cdots \varepsilon_m) \sim l^{(\nu_1)}(\varepsilon_1) \cdots l^{(\nu_m)}(\varepsilon_m), \tag{33}$$

where $l^{(\nu_1)}(\varepsilon_1)$ is the marginal distribution introduced in H. Geiringer (1948a, equation (32)), with ν_1 and ε_1 standing for ν and α used there.

In fact for $m=1$ and with ν and α instead of ν_1 and ε_1, the definition (31) gives

$$l^{(\nu)}(\alpha) = \binom{\nu}{0} l(\alpha) + \binom{\nu}{1} l(\alpha+1) + \cdots + \binom{\nu}{\nu} l(\alpha+\nu). \tag{34}$$

For $s=m=2$ the definitions reduce to those of section 2 of the present paper with the marginal distributions defined in (10), (11), and (13). For the distribution (31) we have

$$\sum_{\varepsilon_1}^{0\ldots s-\nu_1} \cdots \sum_{\varepsilon_m}^{0\ldots s-\nu_m} l^{(\nu_1)\ldots(\nu_m)}(\varepsilon_1 \cdots \varepsilon_m) \cdot \binom{s-\nu_1}{\varepsilon_1} \cdots \binom{s-\nu_m}{\varepsilon_m} = 1, \tag{35}$$

a relation that corresponds to equation (34) in H. Geiringer (1948a). *The symmetry relations for the marginal distribution* (31) follow from (30):

$$l^{(\nu_1)\ldots(\nu_m)}(\varepsilon_1 \cdots \varepsilon_m) = l^{(\nu_1)\ldots(\nu_m)}(s-\nu_1-\varepsilon_1, \cdots, s-\nu_m-\varepsilon_m). \tag{36}$$

For $\nu_1 = \cdots = \nu_m = s-1$, (36) reduces to the symmetry relation (8′) of Geiringer (1944) and for $m=1$ and general "s" to the symmetry relations (33) of Geiringer (1948a) (see also (29)). With these definitions the marginal distribution which corresponds to the normal organism, $s=1$, becomes

$$l^{(s-1)\ldots(s-1)}(\varepsilon_1 \cdots \varepsilon_m) = l_{12\ldots m}(\varepsilon_1 \cdots \varepsilon_m), \qquad (\varepsilon_i = 0, 1). \tag{37}$$

We call it linkage distribution, while for $s > 1$ we speak of the segregation distribution.

Another important particular case is obtained if we put $\nu_1 = \nu_2 \cdots = \nu_{m-1} = 0$, $\nu_m = s$ in (31). This amounts to reducing the number "m" to "$m-1$" without changing the "s" for the first $(m-1)$ factors. The result is a distribution which no longer depends on ε_m:

$$\begin{aligned} &l^{(0)\ldots(0)(s)}(\varepsilon_1 \cdots \varepsilon_{m-1}\, 0) \\ &= \sum_{\eta_m}^{0\ldots s} l(\varepsilon_1 \cdots \varepsilon_{m-1}\, \eta_m) \cdot \binom{s}{\eta_m}, \quad \begin{pmatrix} \varepsilon_i = 0, \cdots, s; \\ i = 1, \cdots, (m-1) \end{pmatrix}, \end{aligned} \tag{38}$$

since, according to (32), $\varepsilon_m = 0$. Finally, applying this type of summation to $(m-1)$ of the m characters we obtain the marginal distributions of order *one*, and general "s" such as

$$l^{(0)(s)\ldots(s)}(\varepsilon_1, 0, \cdots 0) = l_1(\varepsilon_1), \quad (\varepsilon_1 = 0, \cdots, s). \tag{39}$$

This is the s.d. for the first locus which has, because of (36), the required symmetry properties. There is of course such a distribution for each character, such as

$$
\begin{aligned}
&l^{(s)\cdots\cdots(s)(0)(s)\cdots\cdots(s)}(0,\cdots\cdots,0,\varepsilon_i,0,\cdots\cdots,0)\\
&\qquad=l_i(\varepsilon_i),\quad(\varepsilon_i=0,\cdots\cdots,s),
\end{aligned}
\tag{40}
$$

and

$$l_i(\varepsilon_i)=l_i(s-\varepsilon_i). \tag{41}$$

We shall need all these marginal distributions in the proofs of our limit theorems.

It is not difficult to write down any such marginal distribution if we make use of the "symbolical" notation introduced in (33). As an example consider for $s=m=3$:

$$
\begin{aligned}
&l^{(2)(1)(3)}(000)\sim l^{(2)}(0)\,l^{(1)}(0)\,l^{(3)}(0)\\
&=[l_0+2l_1+l_2]\cdot[l_0+l_1]\cdot[l_0+3l_1+3l_2+l_3]\\
&=l(000)+3l(001)+3l(002)+l(003)\\
&\;+l(010)+3l(011)+3l(012)+l(013)\\
&\;+2l(100)+6l(101)+6l(102)+2l(103)\\
&\;.\quad.\quad.\quad.\quad.\quad.\quad.\quad.\quad.\quad.\quad.\quad.\\
&\;+l(210)+3l(211)+3l(212)+l(213),
\end{aligned}
$$

or, in the same way,

$$l^{(2)(1)(3)}(100)\sim[l_1+2l_2+l_3]\cdot[l_0+l_1]\cdot[l_0+3l_1+3l_2+l_3].$$

We finally wish to define *independence* for our general s.d. We shall call $l(\varepsilon_1\,\varepsilon_2\cdots\cdots\varepsilon_m)$, $(\varepsilon_i=0,1,\cdots\cdots s)$ *independent* if

$$l(\varepsilon_1\cdots\cdots\varepsilon_m)=l_1(\varepsilon_1)\cdots\cdots l_m(\varepsilon_m). \tag{42}$$

Here, as we easily see, $l_i(\varepsilon_i)$ are the *marginal distributions* defined in (40). It then follows easily that *if* $l(\varepsilon_1\cdots\cdots\varepsilon_m)$ *resolves into a product, according to* (42) *the same is true for all marginal distributions*

$$l^{(\nu)\cdots\cdots(\nu)}(\varepsilon_1\cdots\cdots\varepsilon_m),\qquad(\varepsilon_i=0,1,\cdots\cdots(s-\nu)),$$

and, eventually,

$$l^{(s-1)\cdots\cdots(s-1)}(\varepsilon_1\cdots\cdots\varepsilon_m)=l_{12\cdots\cdots m}(\varepsilon_1\cdots\cdots\varepsilon_m)=\frac{1}{2^m}. \tag{43}$$

for all combinations $(\varepsilon_1,\cdots\cdots\varepsilon_m)$ *where* $\varepsilon_i=0,1$. It is well known that (43) represents G. Mendel's original assumption of "independent assortment." For $m=1$, general "s", the equation corresponding to (43) is equation (38) in H. Geiringer (1948a). Obviously (42) is satisfied if the $\left[\binom{2s}{s}\right]^m$ *values of the s.d. are all equal to* *each other*; hence each equal to $1 \Big/ \left[\binom{2s}{s}\right]^m$. In this case each $l_{12\cdots m}\,(\varepsilon_1 \cdots \varepsilon_m)$, $(\varepsilon_i = 0\,,\,1)$ of the l.d. equals $1/2^m$ and each $l_i(\varepsilon_i)$, $(\varepsilon_i = 0, 1, \cdots s)$ equals $1 \Big/ \binom{2s}{s}$.

5. *Recurrence Formulas for* m=s=2 .

It seems useful to investigate the recurrence relations for the particular case $m=s=2$ by explicit computation before dealing with the general case in which explicit computation is not possible. We shall denote, as before, by $p^{(n)}(A^{z_1}a^{2-z_1}B^{z_2}b^{2-z_2})$ the probability distribution of gametes in the nth generation with sum equal to one according to (1). From this distribution we derive *two marginal distributions of order three.* Using the variables α_i equal to A or to a, and β_i equal to B or to b, $(i = 1\,,\,2)$, we introduce

$$p_{123}{}^{(n)}(\alpha_1\alpha_2\beta_1) = \sum_{\beta_2} p^{(n)}(\alpha_1\alpha_2\beta_1\beta_2) = p_{124}{}^{(n)}(\alpha_1\alpha_2\beta_2)\,.$$

We may omit the subscripts and have the two distributions

$$p^{(n)}(\alpha_1\alpha_2\beta_1), \quad \text{and} \quad p^{(n)}(\alpha_1\beta_1\beta_2), \tag{44}$$

with

$$\sum_{\alpha_1}\sum_{\alpha_2}\sum_{\beta_1} p^{(n)}(\alpha_1\alpha_2\beta_1) = 1, \quad \sum_{\alpha_1}\sum_{\beta_1}\sum_{\beta_2} p^{(n)}(\alpha_1\beta_1\beta_2) = 1.$$

There are *three marginal distributions of order two,*

$$p^{(n)}(\alpha_1\alpha_2), \qquad p^{(n)}(\alpha_1\beta_1), \qquad p^{(n)}(\beta_1\beta_2), \tag{45}$$

where, e.g.,

$$p^{(n)}(\alpha_1\alpha_2) = \sum_{\beta_1} p^{(n)}(\alpha_1\alpha_2\beta_1) = \sum_{\beta_1}\sum_{\beta_2} p^{(n)}(\alpha_1\alpha_2\beta_1\beta_2)\,;$$

with

$$\sum_{\alpha_1}\sum_{\alpha_2} p^{(n)}(\alpha_1\alpha_2) = 1, \qquad \sum_{\alpha_1}\sum_{\beta_1} p^{(n)}(\alpha_1\beta_1) = 1, \quad \text{etc.}\,;$$

or more explicitly, for example,

$$\begin{aligned} p^{(n)}(A^2) &= p^{(n)}(A^2B) + p^{(n)}(A^2b) \\ &= p^{(n)}(A^2B^2) + 2p^{(n)}(A^2Bb) + p^{(n)}(A^2b^2)\,; \end{aligned}$$

and, finally, *two marginal distributions of order one,*

$$p^{(n)}(\alpha_1), \qquad p^{(n)}(\beta_1), \tag{46}$$

where

$$p^{(n)}(\alpha_1) = \sum_{\alpha_2} p^{(n)}(\alpha_1\alpha_2) = \sum_{\beta_1} p^{(n)}(\alpha_1\beta_1) = \cdots$$
$$= \sum_{\alpha_2}\sum_{\beta_1}\sum_{\beta_2} p^{(n)}(\alpha_1\alpha_2\beta_1\beta_2)\,,$$

and

$$\sum_{\alpha_1} p^{(n)}(\alpha_1) = 1\,, \qquad \sum_{\beta_1} p^{(n)}(\beta_1) = 1.$$

We now wish to derive $p^{(n)}(\alpha_1\alpha_2\beta_1\beta_2)$ or, more specifically, $p^{(n)}(A^2B^2)$ from the distribution of genotypes, $w^{(n)}$, in the nth generation. For this purpose we shall consider each one of the various terms in (2) and multiply it by the corresponding probability values of the s.d. For the sake of brevity let us now write $p^{(n)} = p$, $w^{(n)} = w$, $p^{(n+1)} = p'$, $w^{(n+1)} = w'$. Consider, for example, in accordance with (2) and (3), the term $8w(A^2B^2;\ AaBb)$. If we derive $p(A^2B^2)$ this expression is multiplied by $(\lambda_{22} + 2\lambda_{12} + 2\lambda_{21} + 4\lambda_{11})$ where we write $\lambda_{\alpha\beta}$ for $\lambda(\alpha\,,\beta)$. In fact, λ_{22} is the probability that the four values $AABB$ in $p(A^2B^2)$ are all maternal values; $2\lambda_{12}$ is the probability that of the two A-values one is a maternal, the other a paternal one; while both B-values are maternal heritage, and similarly for $2\lambda_{21}$; finally, $4\lambda_{11}$ is the probability that one A-value will be paternal, the other maternal and the same holds for the B-values. On the other hand, for example, the coefficient of $w(a^2b^2;\ A^2Bb)$ will be zero since (under chromosome segregation) the four values $AABB$ cannot be transmitted by an individual of this type. If we consider each w-probability in this way we find

$$\begin{aligned}
p&(A^2B^2)\\
&= w(A^2B^2;A^2B^2)\cdot 1 + 2w(A^2B^2;A^2b^2)(\lambda_{22} + 4\lambda_{12} + \lambda_{02})\\
&\quad + 2w(A^2B^2;a^2B^2)\cdot(\lambda_{22} + 4\lambda_{21} + \lambda_{20}) + 2w(A^2B^2;a^2b^2)\lambda_{22}\\
&\quad + 4w(A^2B^2;A^2Bb)\cdot(\lambda_{22} + 4\lambda_{12} + \lambda_{02} + 2\lambda_{21} + 8\lambda_{11} + 2\lambda_{01})\\
&\quad + \cdots \\
&\quad + 8w(A^2B^2;AaBb)\cdot(\lambda_{22} + 2\lambda_{12} + 2\lambda_{21} + 4\lambda_{11}) + \cdots\\
&\quad + 16w(A^2Bb;AaBb)\cdot(\lambda_{21} + 2\lambda_{11}) + \cdots\\
&\quad + 16w(AaBb;AaBb)\cdot\lambda_{11}\,.
\end{aligned} \tag{47}$$

There are on the right-hand side of (47) twenty w-values of which eight are written. Note that the coefficients of each w-value are nothing but *marginal probabilities of our s.d.* (see section 2). For example, $\lambda_{22} + 4\lambda_{12} + \lambda_{02} = l_2(2)$, the coefficient of $8w(A^2B^2;AaBb)$ which has been discussed in detail, $(\lambda_{12} + 2\lambda_{12} + 2\lambda_{21} + 4\lambda_{11})$, equals $l_{12}(11)$, while the coefficient of $4w(A^2B^2;A^2Bb)$ is $(\lambda_{22} + 4\lambda_{12} + \lambda_{02} + 2\lambda_{21} + 8\lambda_{11} + 2\lambda_{01}) = l_{12}(11) + l_{12}(01) = 1/2$. It would not be difficult to describe the general structure of this type of formula.

Now we write the same formula for p' and w'. Next, we express $w' = w^{(n+1)}$ in terms of the $p = p^{(n)}$ by means of (4). We obtain a formula similar to (47),

$$p'(A^2B^2) = p(A^2B^2)\, p(A^2B^2) + 2p(A^2B^2)\, p(A^2b^2) \cdot (\lambda_{22} + 4\lambda_{12} + \lambda_{02}) + \cdots .$$

The decisive step is then to rearrange this formula by collecting on the right-hand side those p-products which are multiplied by the same $\lambda_{\alpha\beta}$. Before doing this the coefficient "1" of $p(A^2B^2)\ p(A^2B^2)$ is to be replaced by the sum of all λ-values, using (9). It then turns out that the coefficient of each $\lambda_{\alpha\beta}$ is the product of two marginal probabilities as introduced in (44)—(46). (Note that while *before* the coefficient of each w-value was a marginal probability of the s.d., now the coefficient of each λ-value is the product of two marginal probabilities of the p-distribution.)

The final result is the following simple formula where the λ's have been replaced by the respective l-values in consideration of (5) and (8),

$$\begin{aligned} p'(A^2B^2) = {} & p(A^2B^2)\,[l(00) + l(22)] \\ & + 2p(A)\, p(AB^2)\,[l(10) + l(12)] \\ & + 2p(B)\, p(A^2B)\,[l(01) + l(21)] \\ & + 4p(AB)\, p(AB) \cdot l(11) \\ & + p(A^2)\, p(B^2) \cdot [l(20) + l(02)] . \end{aligned} \tag{48}$$

This formula can be interpreted in the following way:

$$l(\alpha\beta) \cdot \binom{2}{\alpha} \binom{2}{\beta}$$

is the probability that α maternal A-values and β maternal B-values will be transmitted as well as $(s-\alpha)$ paternal A-values and $(s-\beta)$ paternal B-values; $p(A^\alpha B^\beta)$ is the probability of a maternal gamete with α A-values and β B-values; while $p(A^{s-\alpha} B^{s-\beta})$ is the probability of a paternal gamete with $(s-\alpha)$ and $(s-\beta)$ A- and B-values respectively, in the nth generation. Under random breeding the sum over all α and β of products of these three probabilities gives the probability of a gamete of type (A^2B^2) in the $(n+1)$st generation. The corresponding formula for $s=1$, $m=2$ has been given by H. S. Jennings (1917) and the formula for $s=2$, $m=1$ by J. B. S. Haldane (1930). If for $s > 1$, we consider chromatid segregation, the recurrence formulas for $m=1$ and for $m=2$ no longer show this particularly simple structure.

In an analogous way a formula for $p'(AaBb)$ may be derived.

It is easily seen that the structure of these formulas *does not depend on the number of alleles.* If there are more than two alleles for each factor, there will be more terms in the formula which takes the place of (47). However, in the decisive transformation where we determine the coefficient of each $\lambda_{\alpha\beta}$, the sum of all p-products which multiply the same $\lambda_{\alpha\beta}$ will, exactly as before, resolve into the product of the same two marginal probabilities as before since each marginal probability is then defined by summations over r rather than over two terms. The formula (48) and the following formula (49) thus hold with the understanding that A, a as well as B, and b are just any two out of an arbitrary number, r, of alleles. The result is:

$$\begin{aligned} p'(AaBb) = {} & p(AaBb)\,[l(00) + l(22)] \\ & + [p(A)\,p(aBb) + p(a)p(ABb)]\,[l(10) + l(12)] \\ & + [p(B)\,p(Aab) + p(b)\,p(AaB)]\,[l(01) + l(21)] \qquad (49) \\ & + [p(AB)\,p(ab) + p(Ab)\,p(aB)] \cdot 2l(11) \\ & + p(Aa)\,p(Bb) \cdot [l(20) + l(02)]\,. \end{aligned}$$

From (49) we obtain (48) by putting $A{=}a$, $B{=}b$.

Thus the distribution of gametes can easily be computed from generation to generation. The distribution of zygotes then follows for any desired generation by means of (4).

Obviously these formulas are valid for any particular choice of the parameters entering in the definition of the s.d. If for example we consider random chromosome segregation (each λ-value equals 1/36) we obtain:

$$\begin{aligned} 36p' = {} & 2[p(AaBb) + p(Aa)\,p(Bb)] \\ & + 4[p(A)\,p(aBb) + p(a)\,p(ABb) \\ & + p(B)\,p(Aab) + p(b)\,p(AaB)] \\ & + 8[p(AB)\,p(ab) + p(Ab)\,p(aB)]\,, \end{aligned}$$

or, for Haldane's theory, the five l-coefficients in (49) are to be replaced in turn by $q^2/3$, $pq/3$, $pq/3$, $(p^2 + q^2 + pq)/3$, and $p^2/3$.

In the second part of this paper we shall establish an analogous recurrence formula for any "m" and "s". By means of these recurrence formulas we shall investigate the equilibrium problem and the limit behavior for our basic distributions, the distribution of gametes and the distribution of zygotes.

LITERATURE

De Winton, D. and Haldane, J. B. S. 1931. "Linkage in the Tetraploid Primula Sinensis." *Jour. Genetics*, **24**, 121–144.

Fisher, R. A. 1947. "The Theory of Linkage in Polysomic Inheritance." *Phil. Trans. Roy. Soc. London, B.*, **233**, 55–87.

Fisher, R. A. and Mather, K. 1943. "The Inheritance of Style Length in Lythrum Salicaria." *Annals Eugenics,* **12**, 1–23.

Geiringer, H. 1944. "On the Probability Theory of Linkage in Mendelian Heredity." *Ann. Math. Stat.,* **15**, 25–57.

Geiringer, H. 1945. "Further Remarks on Linkage in Mendelian Heredity." *Ann. Math. Stat.,* **16**, 390–398.

Geiringer, H. 1948a. "Contribution to the Heredity Theory of Multivalents." *Jour. Math. and Phys.,* **26**, 246–278.

Geiringer, H. 1948b. "On the Mathematics of Random Mating in Case of Different Recombination Values for Males and Females." *Genetics,* 33, 548–564.

Geiringer, H. 1949. "Chromatid Segregation of Tetraploids and Hexaploids." *Genetics,* November.

Haldane, J. B. S. 1930. "Theoretical Genetics of Autopolyploids." *Jour. Genetics,* **22**, 359–372.

Jennings, H. S. 1917. "The Numerical Results of Diverse Systems of Breeding with Respect to Two Pairs of Characters, etc." *Genetics,* **2**, 97–154.

Mather, K. 1936. "Segregation and Linkage in Autotetraploids." *Jour. Genetics,* **32**, 287–314.

Sansome, F. W. 1933. "Chromatid Segregation in Solanum Lycopersicum." *Jour. Genetics,* **27**, 105–132.

Sansome, F. W. and Philp, K. 1939. *Recent Advances in Plant Genetics.* Second Edition, Philadelphia: The Blakiston Company.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 11, 1949

THE STEADY STATE KINETICS OF SOME BIOLOGICAL SYSTEMS: II

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Steady state kinetic relations previously developed for *closed, homogeneous* systems are extended to *open* systems consisting of geometrically confined regions of arbitrary shape. The generalized system of consecutive reactions is considered to occur within the cell, and the cell plus environment are treated as an open system. The diffusion condition is imposed upon the kinetic solution for various special cases and the method of *general* solution when all products, reactants and intermediates, may enter and leave the cell is indicated.

In a previous paper (Hearon, 1949), hereinafter referred to as I, the system of consecutive reactions

$$\begin{array}{c} C_0 + C_1 \leftrightarrows X_1 + B_1 \\ C_2 + X_1 \leftrightarrows X_2 + B_2 \\ \cdot \qquad\qquad \cdot \\ \cdot \qquad\qquad \cdot \\ \cdot \qquad\qquad \cdot \\ \cdot \qquad\qquad \cdot \\ C_i + X_{i-1} \leftrightarrows X_i + B_i \\ C_n + X_{n-1} \leftrightarrows B_n \end{array} \tag{1}$$

was considered to be in the steady state. As noted in I, this assumption requires that $\frac{d[X_i]}{dt} = 0$ for all i. The vanishing of the time derivative of all $[X_i]$ in turn requires that the concentrations of all reactants $[C_i]$, $i = 0, 1, \cdots n$ and all products $[B_i]$, $i = 1, 2, \cdots n$ must be time independent. (Exceptionally, this restriction may be removed from $[B_n]$ if $k_{-n} = 0$.) These conditions may be achieved in several ways. All the ways discussed in I applied strictly to the "closed systems" considered there. When *in vivo* systems are considered in biology, it is most usual to deal with open systems. In such cases the reactants and products may be maintained constant by supply *to* the system from the environment and flow *from* the system. The situation is then that the system proper is the set of reactions being considered; the reactants are maintained constant by sources in the environment and the products flow to sinks in the environment. These sources and sinks must now have the property that addition or withdrawal of material does not change their levels. This requirement is met physically by having the external concentrations constant by adherence to short experimental times, or by employment of environment of such size that quite regardless of the absolute levels (*concentrations*) the addition or withdrawal of even an appreciable *amount* of material changes the levels only negligibly.

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†This work was done while the author was a Senior Research Fellow of the National Institute of Health.

Of particular interest is the flow of material from the ambient medium into a cell, its conversion there through a set of reactions to products and the flow of products into the medium. In general the reactions will occur only within the cell† and the cell plus environment constitutes an open system into the description of which must enter the parameters governing the flux of matter into and out of the cell. The rate of consumption of any C_i will depend upon the concentration of C_i *in* the system and upon the concentration of every other component *in* the system. The concentration of C_i in the system in turn depends upon the rate of consumption according to the equation (Rashevsky, 1948)

$$[C_i] = [C_i]_0 - \Lambda_{C_i} v_{C_i}, \tag{2}$$

where $[C_i]_0$ is the *external* concentration of C_i, v_{C_i} is the rate of consumption of C_i and Λ_{C_i} is, as defined by N. Rashevsky (1940), the total diffusion resistance of the cell to C_i. In general Λ_{C_i} is a function of the diffusion coefficients of C_i in the medium and in the cell, of the permeability of the cell membrane to C_i and of the major and minor axes of the cell (Rashevsky, 1948). Exactly similar considerations apply to any product B_i and the equation analogous to (2) is

$$[B_i] = [B_i]_0 + \Lambda_{B_i} v_{B_i}. \tag{3}$$

While many systems of this type have been solved (see Rashevsky, 1948) and indeed some rather complicated cases (Landahl, 1939), it seems desirable to attempt to lay down some general formulations based upon the steady state solutions previously discussed (I). The direct procedure, which has been previously used, is to write v_i, equivalent to the *net* rate of an *individual* step in the system (1), for every

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†This statement already implies that certain components, viz., the catalysts involved, may not leave the cell.

C_i, X_i and B_i and to substitute into these relations the corresponding equations (2) and (3) and solve the set for the desired rate. There will be considerable advantage in making use of the steady state solution and solving this with the diffusion equations (2) and (3), since the assumption is always made that the reactions in the cell are in the steady state. This procedure, when it can be used, has the feature that the expression for a given rate will be obtained in a form analogous to the expression for the homogeneous system, thus the effects of diffusion, geometry and size are more readily assessed. This will be illustrated first by solving the simplest possible enzyme system.

The Simple Enzyme System.

Let the mechanism be

$$E+S\leftrightarrows E\cdot S\rightarrow E+p,$$

using the notation of I, and let S and p only leave and enter the cell. The steady state solution is then (equation (10), I)

$$v=\frac{k_2[E_0][S]}{K+[S]}=\frac{V_m[S]}{K+[S]},\tag{4}$$

where

$$K=\frac{k_{-1}+k_2}{k_1}.$$

Equation (2) becomes

$$[S]=[S]_0-\Lambda v,\tag{5}$$

and substitution of (4) into (5) and solving for $[S]$ gives

$$[S]=\frac{[S]_0-a}{2}+1/2\sqrt{([S]_0-a)^2+4K_S[S]_0},\tag{6}$$

where $a=K+\Lambda V_m$. Using (6) in (4) gives

$$\begin{aligned}q&=\frac{V_m([S]_0-\Lambda v)}{K_S+([S]_0-\Lambda v)}\\&=\frac{V_m\left\{\dfrac{[S]_0-a}{2}+1/2\sqrt{([S]_0-a)^2+4K_S[S]_0}\right\}}{K_S+\left\{\dfrac{[S]_0-a}{2}+1/2\sqrt{([S]_0-a)^2+4K_S[S]_0}\right\}}.\end{aligned}\tag{7}$$

Here and elsewhere we will denote by q the diffusion conditioned rate and by v the simple kinetic solution such as (4). From (7) it is seen that if $[S]_0$ is large,

$$q = \frac{V_m[S]_0}{K_S + [S]_0}, \tag{8}$$

which is identical with v from (4) with $[S] = [S]_0$. From (4) and (8) it follows that the limiting velocity V_m is the same for q and v. The conditions for (8) may also be that Λ is small (D_i large, h large) or that v is inherently small (k_2 small or $[E]_0$ small). Equation (8) then becomes the analytical statement of the fact that if the total permeability, $\lambda = 1/\Lambda$ (Rashevsky, 1940), is large or if the rate of consumption is small, then $[S] \sim [S]_0$ and v and q do not differ.

Conversely, if Λ is large or if v is inherently large, then from (5), $[S] \sim 0$, and

$$q = \lambda[S]_0. \tag{9}$$

In this case diffusion is completely limiting in the sense that the observed q is simply the rate of diffusion into the cell and does not contain the parameters, K and V_m, of the system proper.

An intermediate case which exhibits a point which should be noted is: If $[S]$ is small ($K >> [S]$), then from (4) and (5)

$$[S] = \frac{[S]_0}{1 + \frac{\Lambda V_m}{K}}, \tag{10}$$

and (10) into (4) gives

$$q = \frac{V_m}{K}\left(\frac{[S]_0}{1 + \frac{\Lambda V_m}{K}}\right). \tag{11}$$

From (11) it is clear that if either Λ or $V_m (= k_2[E_0])$ becomes large, (11) reduces to (9), but as Λ continues to increase $q \to 0$ while the limit of q as $V_m \to \infty$ is given by (9). The above discussion is given in some detail because analogous cases will arise in the more general systems to be discussed. Finally it will be indicated how the parameters K and Λ may be determined in this simple case. From (4) it is seen that if $[S] = K$, then $v = \frac{1}{2} V_m$ and that the initial slope of the v vs. $[S]$ curve is given by

$$\left(\frac{\partial v}{\partial [S]}\right)_{[S]=0} = \frac{V_m}{K}. \tag{12}$$

From (5) when $v = \frac{1}{2} V_m$ the required external concentration, $[S]_0^{(1/2)}$, is given by

$$[S]_0^{(1/2)} = K + \frac{\Lambda V_m}{2}. \tag{13}$$

Thus while v and q exhibit the same limiting velocity V_m, v reaches $\frac{1}{2} V_m$ at $[S] = K$ and q reaches $\frac{1}{2} V_m$ at

$$[S]_0 = K + \frac{\Lambda V_m}{2},$$

i.e., the external concentration $[S]_0$ must exceed the internal concentration $[S]$ by the amount $\frac{\Lambda V_m}{2}$. The initial slope of the q vs. $[S]_0$ curve is

$$\left(\frac{\partial q}{\partial [S]_0}\right)_{[S]_0=0} = \frac{V_m}{K + \Lambda V_m} \equiv m_0. \tag{14}$$

From (13) and (14) the values of K and Λ are obtained as

$$\begin{aligned} K &= \frac{2\,[S]_0^{(1/2)} m_0 - V_m}{m_0}; \\ \Lambda &= 2\left(\frac{1}{m_0} - \frac{[S]_0^{(1/2)}}{V_m}\right). \end{aligned} \tag{15}$$

The above analysis supposes that V_m may be observed directly, i.e., when q becomes independent of $[S]_0$ at large values of $[S]_0$ it is assumed that this value of q is V_m. In practice this assumption is not always a good one even for isolated enzyme systems (see, for example, Lipmann, 1939).

The General System with C_1 *Diffusible.*

In this case consider that only C_1 diffuses into the cell from outside; all other components of the system are confined to the cell except the final product B_n. If the final step is irreversible, $k_{-n} \equiv 0$, it is immaterial that B_n is diffusible. The condition (2) which is here

$$[C_1] = [C_1]_0 - \Lambda_{C_1} v \tag{16}$$

is easily included in the problem by writing the first member of the set (2) from I as

$$1 + k_1 \Lambda_{C_1} [C_0] = w_1^0 \alpha_0 - w_{-1} \alpha_1, \tag{17}$$

where $w_1{}^0 = k_1[C_0][C_1]_0$ and the α's are as defined in I. Equation (17) results from the substitution of (16) into the definition of w_1 in (1) of I. The problem may also be solved more directly by writing the general solution of the system (see equation (3) of I) as

$$v = \frac{w_1 \prod\limits_{i=2}^{n} w_i}{\phi}, \tag{18}$$

where $\phi = w_2 w_3 \cdots\cdot w_n + w_{-1} w_3 \cdots\cdot w_n + \cdots\cdot + w_{-1} w_{-2} \cdots\cdot w_{-(n-1)}$ is the denominator of (3) of I and $w_1 = k_1[C_1][C_0]$. From (16) and (18)

$$[C_1] = \frac{[C_1]_0}{1 + \beta/\phi}, \tag{19}$$

where

$$\beta = \Lambda_{C_1} k_1 [C_0] \prod_{i=2}^{n} w_i .$$

Substituting (19) into (18) gives

$$\begin{aligned} q &= \frac{k_1[C_0][C_1]_0 \prod\limits_{i=2}^{n} w_i}{(1 + \beta/\phi)\phi} \\ &= \frac{w_1{}^0 w_2 w_3 \cdots\cdot w_n}{(1 + k_1 \Lambda_{C_1}[C_0]) w_2 w_3 \cdots w_n + w_{-1} w_3 \cdots w_n + \cdots\cdot + w_{-1} \cdots w_{-(n-1)}} . \end{aligned} \tag{20}$$

Equation (20) differs from equation (18) only in that the first term in ϕ has been multiplied by $1 + k_1 \Lambda_{C_1}[C_0]$. It will be noted from (18) and (20) that while v is linear in $[C_0]$, q exhibits a limiting velocity when $[C_0]$ is increased indefinitely. This limiting velocity is $\lambda_{C_1}[C_1]_0$. The interpretation is clear and is in accord with the general principles set forth in I. When $[C_0]$ is increased, the rate of the first step, and hence of the entire system, cannot exceed the rate at which C_1 can diffuse into the cell; the rate is $\lambda_{C_1}[C_1]_0$. The dependence of q on C_i, $i \geq 2$, differs in an obvious manner from that of v. For example, the limit of q when $[C_2] \rightarrow \infty$ is

$$\frac{w_1{}^0}{1 + k_1 \Lambda_{C_1}[C_0]},$$

while the limit of v is simply w_1.

The General System with C_i *Diffusible;* $i \neq 0, 1$.

The same considerations apply here as in the above case, viz., only a particular C_i diffuses into the cell and the final product B_n diffuses out; it is again assumed that $k_{-n} = 0$. The general solution for v from (18) may be written as

$$v = \frac{\prod_{i=1}^{n} w_i}{\sum_{i}^{n} T_i}, \tag{21}$$

where the T_i are the additive terms of ϕ; there will be n such terms, each the product of $n - 1$ w's. The terms T_1 through T_{i-1} will contain w_i as a factor. Thus (21) may be written as

$$v = \frac{\prod_{i=1}^{n} w_i \Big/ \sum_{\xi=1}^{i-1} \frac{T_\xi}{w_i}}{w_i + \sum_{\xi=i}^{n} T_\xi \Big/ \sum_{\xi=1}^{i-1} \frac{T_\xi}{w_i}}. \tag{22}$$

Since the terms T_1 through T_{i-1} will always contain $w_{i+1} w_{i+2} \cdots\cdot w_n$ as a factor, it can be shown that the denominator of (22) is

$$w_i \left\{ \frac{w_1 w_2 \cdots\cdot w_{i-1}}{(w_2 w_3 \cdots w_{i-1}) + (w_{-1} w_3 \cdots w_{i-1}) + \cdots + w_{-1} w_{-2} w_{-3} \cdots w_{-(i-2)}} \right\}. \tag{23}$$

The expression in the brackets is just $V_{1,\, i-1}$ as defined in I. For reasons that will become obvious it will be denoted here by $V_m^{(C_i)}$. Then

$$\left. \begin{aligned} v &= \frac{V_m^{(C_i)} [C_i]}{[C_i] + \Phi_i}; \\ \Phi_i &\equiv \frac{\sum_{\xi=i}^{n} T_\xi}{k_i \sum_{\xi=1}^{i-1} T_\xi / w_i} \end{aligned} \right\}. \tag{24}$$

It is now obvious that $V_m^{(C_i)}$ is the limiting velocity for C_i and may be obtained at once from (21). The general expression Φ_i can be obtained by deleting $[C_i]$ from the sum of those T terms which contains it as a factor and dividing the sum of the remaining terms by k_i times the result. With v in the form (24) the condition $[C_i] = [C_i]_0 - \Lambda_{C_i} v$

may be straightforwardly imposed. The solution of

$$[C_i] = [C_i]_0 - \frac{\Lambda_{C_i} V_m^{(C_i)} [C_i]}{[C_i] + \Phi_i} \tag{25}$$

is

$$[C_i] = \frac{[C_i]_0 - (\Phi_i + \Lambda_{C_i} V_m^{(C_i)})}{2} + \frac{\sqrt{\{[C_i] - (\Phi_i + \Lambda_{C_i} V_m^{(C_i)})\}^2 + 4[C_i]_0\,\Phi_i}}{2}. \tag{26}$$

Using (26) in (24) gives

$$q = \frac{V_m^{(C_i)}\,\{G + H\}}{2\Phi_i + \{G + H\}}, \tag{27}$$

where $G = [C_i]_0 - (\Phi_i + \Lambda_{C_i} V_m^{(C_i)})$ and $H = \sqrt{G^2 + 4[C_i]_0\Phi_i}$.

This form may be briefly discussed as follows: When $[C_i]_0 \to \infty$, $q \to V_m^{(C_i)}$ as expected from the mode of derivation of (27). When Λ_{C_i} is small, q becomes

$$q = \frac{V_m^{(C_i)}[C_i]_0}{[C_i]_0 + \Phi_i}, \tag{28}$$

which is formally identical with the same situation for the simple case (equation (8)). When Λ_{C_i} becomes large,

$$q = \lambda_{C_i}[C_i]_0; \tag{29}$$

identical with (9) for the simple case. As in the simple case there is an intermediate situation analogous to (11).

When the dependence of q upon $[C_k]$ is considered, one must distinguish between the cases in which $k > i$ and $k < i$.

When $[C_k]$, $k > i$, is increased indefinitely, the only quantity in q which varies is Φ_i. It is easily shown that Φ_i approaches the Φ_i for the first $k - 1$ steps of the system and q approaches the corresponding q. Since

$$\Phi_i = \frac{1}{k_i w_i} \cdot \frac{T_i + T_{i+1} + T_{i+2} \cdots T_n}{T_1 + T_2 + \cdots + T_{i-1}} \tag{30}$$

and only the terms T_1 through T_{k-1} contain $[C_k]$,

$$\operatorname*{Lim}_{[C_k]\to\infty} \Phi_i = \frac{1}{k_i w_i} \frac{T_i + T_{i+1} \cdots\cdot T_{k-1}}{T_1 + T_2 \cdots\cdot T_{i-1}}. \tag{31}$$

Both numerator and denominator of (31) contain $w_k w_{k+1} \cdots\cdot w_n$ as a factor, and comparison of (30) and (31) shows that the limit (31) is just Φ_i for a system of $k - 1$ steps. If $\Phi_i{}^{(n)}$ is Φ_i as defined for a system of n steps, then

$$\operatorname*{Lim}_{[C_k]\to\infty} \Phi_i{}^{(n)} = \Phi_i{}^{(k-1)}, \qquad k > i. \tag{32}$$

When $[C_k]$, $k < i$, $k \neq 1$ is increased indefinitely, $\Phi_i{}^{(n)}$ becomes zero as is clear from (30), and from (23) $V_m{}^{(C_i)}$ becomes $V_m{}^{(C_k)}$. These particular values in (27) give the corresponding q. If $k = 1$ and $[C_k]$ becomes indefinitely large, from (27) q takes the indeterminate form

$$\frac{\infty \cdot 0}{2\Phi_i{}^{(n)}};$$

for from (26) $[C_i]$ becomes zero and from (23) $V_m{}^{(C_1)} = \infty$. It is easily seen, however, that from $[C_i] = [C_i]_0 - \Lambda_{C_i} v$ the actual limit is

$$q = \lambda_{C_i} [C_i]_0. \tag{33}$$

In summary then

$$\operatorname*{Lim}_{[C_i]_0\to\infty} q = V_m{}^{(C_i)}$$

$$\operatorname*{Lim}_{[C_k]\to\infty} q(\Phi_i{}^{(n)}, V_m{}^{(C_i)}) \left\{ \begin{array}{ll} q(\Phi_i{}^{(k-1)}, \quad V_m{}^{(C_i)}) & k > i \\ q(\Phi_i{}^{(n)} = 0, V_m{}^{(C_k)}) & k < i \\ & k \neq 1 \\ \lambda_{C_i} [C_i]_0 & k = 1. \end{array} \right. \tag{34}$$

The above cases, C_1 diffusible, C_i, $i \neq 1$ diffusible, and the simple enzyme system are of somewhat restricted applicability in that many common systems are such that several C_i and several B_i (produced in a *reversible* step) are diffusible. It should be noted, however, that if a single diffusible substrate is being utilized through a typical dehydrogenase system as discussed in I, this corresponds to the case C_1 diffusible; for the enzyme, the complex $E \cdot S$ and the high molecular weight carrier, (such as flavoprotein) are certainly confined to the cell. The only requirements are that the permeability to the coenzyme be such that its flow from the cell is negligible and that the product is produced in an *irreversible* step. In practice these are frequently good assumptions. Similarly if certain reactions precede the step in which the diffusible substrate enters, this corresponds to the case of any C_i diffusible. The case of enzyme systems with dissociable prosthetic groups treated in I may be handled as the simple enzyme system, for equation (46) of I may be put in a form which is formally identical with equation (4) of this paper. The method of solution is identical with that given here and it is only necessary to replace V_m and K in equations (4), (6), (7), (10) and (11) by the appropriate quantities gotten from (46) of I.

Any C_1 *and any* B_k *Diffusible.*

In the general solution for v, $[C_i]$ and $[B_k]$ occur only in w_i and w_{-k} and v may be put in a convenient form for simultaneous solution with equations (2) and (3). The form depends so strongly upon the position in the system of C_i and B_k that only the method of solution will be indicated. Consider a system of four steps with $k_{-4} = 0$. The expression for v is

$$v = \frac{w_1 w_2 w_3 w_4}{w_2 w_3 w_4 + w_{-1} w_3 w_4 + w_{-1} w_{-2} w_4 + w_{-1} w_{-2} w_{-3}}. \qquad (35)$$

If only C_1 and B_2 are diffusible then (35) may be written

$$v = \frac{[C_1]L}{M + [B_2]N}. \qquad (36)$$

Substitution of (37)

$$\left.\begin{aligned} [C_1] &= [C_1]_0 - \Lambda_{C_1} v \\ [B_2] &= [B_2]_0 + \Lambda_{B_2} v \end{aligned}\right\} \qquad (37)$$

into (36) gives a quadratic in v which may be solved for v in terms of the Λ's and external concentrations of C_1 and B_2. It is clear that many combinations of B's and C's diffusible may be solved in this manner. The manner in which the positions of B_k and C_i in the system influence the degree of the equation to be solved raises an interesting question. The answer in a *given* case is immediately obtained from inspection of (35); as yet no general answer has been obtained. For example, the following table gives the degree of the equation in v for all possible combinations in the system under discussion when any C_i and B_k are diffusible.

i	k	degree
1	1, 2 or 3	quadratic
2	”	”
3	1	cubic
3	2 or 3	quadratic
4	1 or 2	cubic
4	3	quadratic

Similar considerations apply when more than one C and one or more B are diffusible.

The General System, X_i *Diffusible.*

Again the perfectly general case has not been worked out but the method will be clear from the example given below.

If X_1 is diffusible consider the steady state requirement

$$\frac{d[X_1]}{dt} = w_1 - w_{-1}[X_1] - w_{+2}[X_1] + w_{-2} X_2 - \Gamma(X_1) = 0, \quad (38)$$

where $\Gamma(X_1)$ is the flow of X_1 from the cell. From (38)

$$w_1 - w_{-1}[X_1] = w_2[X_1] - w_{-2}[X_2] + \Gamma(X_1). \quad (39)$$

Also in the steady state

$$\left.\begin{aligned} v &= w_1 - w_{-1}[X_1] \\ &= w_2[X_1] - w_{-2}[X_2] + \Gamma(X_1) \\ &= w_3[X_2] - w_{-3}[X_3] \\ &\cdots\cdots\cdots\cdots \\ &= w_n[X_{n-1}] - w_{-n}\,. \end{aligned}\right\} \quad (40)$$

The quantity $\Gamma(X_1)$ is now given by

$$\Gamma(X_1) = \lambda_{X_1}([X_1] - [X_1]_0), \quad (41)$$

where $\lambda_{X_1} = \Lambda_{X_1}^{-1}$ and $[X_1]_0$ is the external concentration of X_1. Taking the case in which $n = 3$ and $k_{-3} = 0$, (40) becomes

$$\left.\begin{aligned} 1 &= w_1\alpha_0 - w_{-1}\alpha_1 \\ 1 &= (w_2 + \lambda_{X_1})\alpha_1 - w_{-2}\alpha_2 - \lambda_{X_1}[X_1]_0\alpha_0 \\ 1 &= w_3\alpha_2\,, \end{aligned}\right\} \quad (42)$$

which is the set corresponding to (2) in I; the notation used here is the same as that in I. The solution of (42) for $v = 1/\alpha_0$ which in our notation will be called q is

$$q = \frac{w_1(w_2 + \lambda_{X_1})w_3 - w_{-1}w_3[X_1]_0\lambda_{X_1}}{(w_2 + \lambda_{X_1})w_3 + w_{-1}w_3 + w_{-1}w_{-2}}. \tag{43}$$

Equation (43) differs from the corresponding expression for v (obtained from (43) by setting $\lambda_{X_1} = 0$) in that w_2 is replaced by $w_2 + \lambda_{X_1}$ and the subtractive term in $[X_1]_0$ appears in the numerator. Similarly, if C_1 and X_2 are diffusible the set corresponding to (42) becomes

$$\left.\begin{aligned} 1 + k_1\Lambda_{C_1}[C_0] &= w_1{}^0\alpha_0 - w_{-1}\alpha_1 \\ 1 &= w_2\alpha_1 - w_{-2}\alpha_2 \\ 1 &= (w_3 + \lambda_{X_2})\alpha_2 - \lambda_{X_2}[X_2]_0\alpha_0, \end{aligned}\right\} \tag{44}$$

where the first member of the set was obtained by using equation (17). The solution of (44) is

$$q = \frac{w_1{}^0w_2(w_3 + \lambda_{X_2}) - w_{-1}w_{-2}\lambda_{X_2}[X_2]_0}{(1 + k_1[C_0]\Lambda_{C_1})(w_3 + \lambda_{X_2})w_2 + w_{-1}(w_3 + \lambda_{X_2}) + w_{-1}w_{-2}}. \tag{45}$$

It is readily seen that if all of the X's are diffusible, the set (40) becomes

$$\begin{aligned} v &= w_1 - w_{-1}[X_1] \\ &= w_2[X_1] - w_{-2}[X_2] + \Gamma(X_1) \\ &= w_3[X_2] - w_{-3}[X_3] + \Gamma(X_2) + \Gamma(X_1) \\ &\quad \cdots\cdots\cdots\cdots\cdots \\ &= w_n[X_{n-1}] - w_{-n} + \sum_{i=1}^{n-1} \Gamma(X_i). \end{aligned} \tag{46}$$

It is also obvious that if in addition to any number of X's one or more C's and B's are considered diffusible, the equations (2) and (3) may be substituted into the corresponding w's in (46). The solution of (46) then gives the perfectly general case. From (46) it is evident that only the first member will be linear under all conditions but the set can in principle be solved systematically; the exact method will depend upon the case at hand. It should be noted that the diffusibility of the X's does not influence the linearity of the members of (46); the diffusibility of any B and C except C_1 causes the nonlinearity of the corresponding member of the set (46).

LITERATURE

Hearon, J. Z. 1949. "The Steady State Kinetics of Some Biological Systems: I." *Bull. Math. Biophysics*, 11, 29–50.

Landahl, H. D. 1939. "Mathematical Biophysics of Cell Respiration: II." *Bull. Math. Biophysics*, 1, 1–16.

Lipmann, F. 1939. "An Analysis of the Pyruvic Acid Oxidation System." *Symp. Quant. Biol.*, 7, 248.

Rashevsky, N., and Landahl, H. D. 1940. "Permeability of Cells, its Nature and Measurement from the Point of View of Mathematical Biophysics." *Symp. Quant. Biol.*, 8, 9–16.

Rashevsky, N. 1948. *Mathematical Biophysics*. Second Edition. Chicago: University of Chicago Press.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 11, 1949

A DIFFUSION PROBLEM

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When two polished metal spheres in contact with each other are immersed in a corrosive solution, their surfaces gradually corrode, leaving, however, a non-corroded zone around the point of contact. The size of this zone is a function of the size of the spheres, concentration of the corrosive, and of the time. The phenomenon has been first observed by F. C. Besic on human teeth immersed in hydrochloric acid, and studied on metal balls. In the present paper it is shown that such a phenomenon may be due to gradients of concentration of the corrosive in the neighborhood of the point of contact, caused by the chemical reaction which consumes the corrosive. Approximate expressions for the size of the uncorroded zones as a function of the size of the balls and as a function of time are derived and found to be in fair agreement with F. C. Besic's data.

It has been observed by F. C. Besic (unpublished) that when extracted teeth were immersed in various acid solutions, all of them showed an area one to two millimeters in diameter that was devoid of corrosion around the point where the crown of the tooth touched the beaker in which it was placed. A similar phenomenon was noted when two teeth were placed in contact with each other and immersed in acid. In all cases the uncorroded area was definitely larger than the area of possible contact.

It has been suggested that the phenomenon was due to a sufficient drop of concentration of the acid in the narrow space between the teeth, around the point of contact. The acid was used up by the corrosion reaction on the surface of the teeth. Because of the narrowness of the space in the immediate neighborhood of the point of contact, the amount of acid diffusing into that space may be insufficient to cover the shortage created by the reaction.

To investigate the phenomenon under better controlled geometrical and physicochemical conditions, the use of steel balls of different diameters in contact with each other was suggested. Hydrochloric acid of different concentrations was used as a corrosive. In this way F. C. Besic investigated the variation of the size of the uncorroded zone as a function of the concentration of the acid, the time, and the size of the balls.

A separate study of the rate of corrosion of steel by hydrochloric acid was also made by F. C. Besic for the purpose of the present study. The result indicates that the rate, q, of consumption of HCl expressed in gm cm^2 sec^{-1}, when plotted against the concentration, c, of the acid, gives a curve convex downward. The accuracy of the measurements was insufficient to establish exactly the form of the function

$$q = f(c). \tag{1}$$

In the present study we shall put, as a very rough approximation,

$$f(c) = kc^2. \tag{2}$$

Since the acid is consumed only at the surface of the steel balls, everywhere in the solution we have

$$\nabla^2 c = 0. \tag{3}$$

Denoting by D the diffusion coefficient, and by ν the normal to the surface, positive when directed outward, we have at the surface of the balls

$$D \frac{\partial c}{\partial \nu} + kc^2 = 0. \tag{4}$$

Considering the size of the beaker as very large compared to the size of the balls, a condition satisfied in the experiments of F. C. Besic, we have at infinity

$$c = c_0 = (\text{const}). \tag{5}$$

Because of the nonlinearity of the boundary condition (4), and because of the peculiar shape of our boundary, an exact solution of the system (3)—(5) is not to be hoped for. The use of the approximation method (Rashevsky, 1948) is indicated.

Let the two balls be of the same radius, R. Using the notations of Figure 1, we have

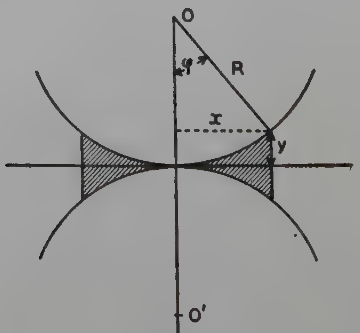

FIGURE 1

$$x = R\sin\phi; \qquad \sin\phi = x/R. \tag{6}$$

We also have

$$y = R(1-\cos\phi). \tag{7}$$

The area, S, of the cylinder of radius x and heighth $2y$ is equal, because of (6) and (7), to

$$S = 4\pi xy = 4\pi R^2 \sin\phi(1-\cos\phi). \tag{8}$$

Equations (6) and (7) also give

$$y = R\left(1-\sqrt{1-\frac{x^2}{R^2}}\right). \tag{9}$$

If x/R is small, as is actually the case in the uncorroded region, we may expand the radical, keeping only the lowest power terms. This gives

$$y = \frac{1}{2}\frac{x^2}{R}. \tag{10}$$

Approximation (1) holds fairly well up to $x/R = \frac{1}{2}$, since $x^4/R^4 = 1/16$. As a very rough approximation, we shall assume it to hold in the whole range, $0 \leq x \leq R$.

The element ds of area of the spherical zone between ϕ and $d\phi$ is, because of equation (6):

$$ds = 2\pi R^2 \sin\phi \, d\phi = \frac{2\pi x\,dx}{\sqrt{1-x^2/R^2}}. \tag{11}$$

For sufficiently small values of x/R, we have approximately

$$ds = 2\pi x\,dx, \tag{12}$$

or,

$$s = \pi x^2. \tag{13}$$

Equations (8) and (10) give

$$S = 2\pi x^3/R. \tag{14}$$

Consider the space limited by the two spheres and the cylinder (Figure 1, shaded). If $\bar{c}$ denotes the average concentration in that space, then, neglecting possible gradients in the direction of the axis, $00'$, we have for the total rate of consumption of the acid, from (2) and (13)

$$2\pi x^2 k\bar{c}^2. \tag{15}$$

If c is the concentration at the surface of the cylinder (also considered as constant at all points of that surface), then the average gradient is

$$2(c-\bar{c})/x\,, \tag{16}$$

and the total inflow, because of (14),

$$2DS(c-\bar{c})/x=4\pi Dx^2(c-\bar{c})/R\,. \tag{17}$$

In a stationary state (15) and (17) must be equal. Equating (15) and the right-hand side of (17), we find:

$$kR\bar{c}^2+2D\bar{c}-2Dc=0\,, \tag{18}$$

or,

$$\bar{c}=\frac{(\sqrt{1+2kRc/D}-1)D}{kR}. \tag{19}$$

The other root of (18) is negative, and, therefore, has no physical meaning.

To obtain a second approximation, we shall now set the *exact* average inflow at x, that is, $DS(dc/dx)$ equal to the average consumption inside of the considered volume, $2\pi x^2k\bar{c}^2$. The first expression is equal, because of (14), to

$$\frac{2\pi Dx^3}{R}\frac{dc}{dx}. \tag{20}$$

The second expression is equal, because of (19), to

$$\frac{2\pi x^2(\sqrt{1+2kRc/D}-1)^2D^2}{kR^2}. \tag{21}$$

Equating (20) to (21) we find:

$$\frac{dc}{dx}=\frac{D(\sqrt{1+2kRc/D}-1)^2}{kRx}, \tag{22}$$

or, by denoting by K an integration constant:

$$\int\frac{dc}{(\sqrt{1+2kRc/D}-1)^2}+K=\frac{D}{kR}\log x\,. \tag{23}$$

The integral in (23) can be readily evaluated by using the substitution

$$\sqrt{1+2kRc/D}-1=y\,. \tag{24}$$

After simple rearrangements, we finally obtain, with $A = \exp. \frac{KkR}{D}$:

$$x = A\left(\sqrt{1 + 2kRc/D} - 1\right) e^{-\frac{1}{\sqrt{1+2kRc/D}-1}} . \tag{25}$$

When $x = R$, the concentration, c, is practically equal to c_0; therefore, A is evaluated by the requirement that for $c = c_0$, $x = R$. This gives finally:

$$x = R \frac{\sqrt{1 + 2kRc/D} - 1}{\sqrt{1 + 2kRc_0/D} - 1} e^{\frac{1}{\sqrt{1+2kRc_0/D}-1} - \frac{1}{\sqrt{1+2kRc/D}-1}} . \tag{26}$$

Apparently a minimum corrosion of steel is necessary in order to become noticeable. For a given time, t, we need a given concentration c^* to achieve this. Since the rate of corrosion is approximately proportional to c^{*2}, approximately,

$$c^{*2}t = \alpha^2 (= \text{const}). \tag{27}$$

Hence, the radius, x_0, of the uncorroded zone is obtained by putting in (26):

$$c = c^* = \alpha/\sqrt{t}. \tag{28}$$

We thus obtain

$$x_0 = R \frac{\sqrt{1 + 2kR\alpha/D\sqrt{t}} - 1}{\sqrt{1 + 2kRc_0/D} - 1} e^{\frac{1}{\sqrt{1+2kRc_0/D}-1} - \frac{1}{\sqrt{1+2kR\alpha/D\sqrt{t}}-1}} . \tag{29}$$

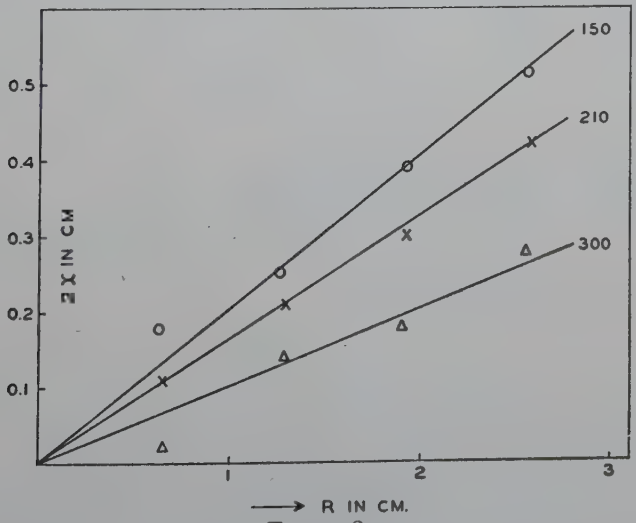

FIGURE 2

For fixed values of c_0 and t, x_0 varies approximately linearly with R. This is borne out by experiments as can be seen from Figure 2. The latter was obtained from graph 3 of F. C. Besic's paper by plotting the values of the diameter of the zone against the values of R for three different relative values of the concentration.

In all of F. C. Besic's experiments the uncorroded zone consisted of two concentric parts: the inner and the outer zone. The outer zone, while not appreciably corroded did not show the brilliant smoothness of the inner one. An explanation of this phenomenon apparently requires a more detailed analysis than the one given here. In line with the approximation assumed in (27), our x_0 refers to the radius of the outer zone. Empirically it is found that the radius of the two zones are approximately proportional to each other, and therefore the same relations hold roughly for both. As t increases, x_0 decreases. For very small values of t, x_0 varies as

$$x_0 \propto \frac{1}{\sqrt[4]{t}} \exp\left(-\beta/\sqrt[4]{t}\right). \tag{30}$$

For large values of t

$$x_0 \propto \frac{1}{\sqrt{t}} e^{-\gamma\sqrt{t}}. \tag{31}$$

The available data are not uniform enough to compare with the equation (29). They show, however, a general conformity with (31).

For constant R and t, x_0 decreases with c_0, in qualitative agreement with experiments. For very large values of c_0,

$$x_0 \propto \frac{1}{\sqrt{c_0}} e^{a/\sqrt{c_0}}, \tag{32}$$

that is, x_0 tends to zero asymptotically.

If, instead of (2), we assume a linear relation

$$f(c) = pc, \tag{33}$$

then by the same method, we find

$$x_0 = R\left(\frac{\alpha}{c_0\sqrt{t}}\right)^{\frac{pR+2D}{2pR}}. \tag{34}$$

Putting

$$\frac{pR+2D}{2pR} = \mu, \tag{35}$$

we have

$$\log x_0 = \text{const} - \frac{\mu}{2} \log t + \log R. \tag{36}$$

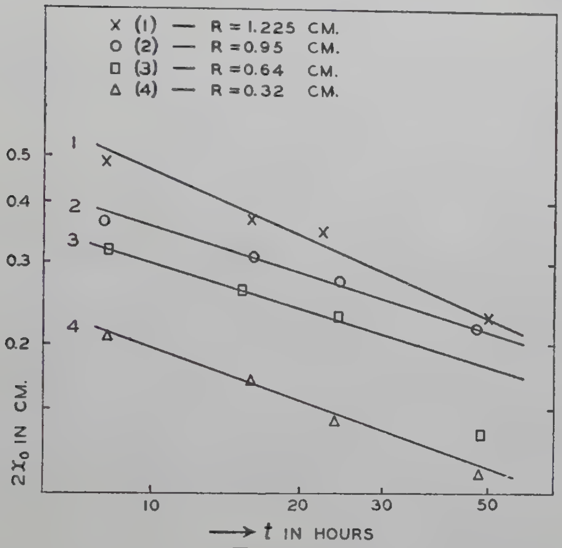

FIGURE 3

Assuming that relation (33) holds approximately for small values of c_0 (large pH), we may compare (36) with available data. Figure 3 shows x_0 vs. t on semi-log paper for $pH = 3$, which is the next highest used. This figure is drawn from data obtained from graph 5 of F. C. Besic's paper, and refers to the inner zone since data for the outer zone are not available. In figure 3 we have $R = 0.32$, $\mu = 0.4$. Taking $p = 3 \times 10^{-4}$ cm sec^{-1} and $D = 2 \times 10^{-5}$ cm^{2}sec^{-1}, we find, from (35), $\mu = 0.7$, which is of the correct order of magnitude.

LITERATURE

Rashevsky, N. 1948. *Mathematical Biophysics.* Second Edition. Chicago: University of Chicago Press.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 11, 1949

MATHEMATICAL BIOLOGY OF SOCIAL BEHAVIOR

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When an individual grows up in a society, he learns certain behavior patterns which are "accepted" by that society. He may in general have a tendency toward behavior patterns other than those which are "accepted" by the society. This tendency toward such unaccepted behavior may be due to a process of cerebration which results in doubt as to the "correctness" of the accepted behavior. Thus, on the one hand, the individual learns to follow the accepted rules almost automatically; on the other hand, he may tend to consciously break those rules. Using a neural circuit, suggested by H. D. Landahl in his theory of learning, a neurobiophysical interpretation of the above situation is outlined. Mathematical expressions are derived which describe the social behavior of an individual as a function of his age, social status, and some neurobiophysical parameters.

In our previous writings (for a summary see Rashevsky, 1948a) we pointed out that a logical extension of the mathematical biology of behavior leads into mathematical sociology. The environmental parameters, which determine some of our reactions, are themselves determined by the reactions of other individuals. Thus we are led from the "problem of one individual" to the more general "problem of n individuals," and thence into the domain of social sciences.

In our book (Rashevsky, 1948a) we attempted to construct a mathematical system of social sciences by starting with some plausible postulates about the interactions of two or more individuals. In principle those postulates should be derived from the equations of the mathematical biology of the central nervous system. As a temporary expedient, these postulates were introduced *de novo* with the hope that they would eventually be reduced to the already more familiar concepts of mathematical biology. This paper represents an attempt at such a reduction.

As has been discussed elsewhere (Rashevsky, 1948b, p. 564), reactions of an individual to any given situation may be mediated through a number of "parallel circuits." Mediation through a "subcortical" circuit results in reactions which are of the nature of simple reflexes or habits. Mediation through a "cortical" circuit results in reactions which are characterized by rational choices through thinking. In line with the general mathematical theory of the central nervous system (Rashevsky, 1948b), we shall consider that all of these parallel circuits mutually inhibit each other. Generalizing the picture still further, we may consider the case in which each circuit contains a "reinforcing" mechanism, such as described originally by N. Rashevsky, and subsequently developed in detail by H. D. Landahl (Householder and Landahl, 1945; Rashevsky, 1948b, chap. xli). This reinforcing mechanism results either in a facilitation or in an inhibition of transmission along a circuit by previous transmissions. On the basis of this picture a theory of learning has been developed by H. D. Landahl, and successfully applied to experimental data.

An individual in a society is usually confronted with the choice of two behavior types: One is the behavior pattern which is considered to be "accepted" by the society; the other is any behavior pattern which goes more or less against the "accepted" standards. From infancy the individual is taught to behave "correctly," that is, in accordance with the accepted pattern. In the course of learning, correct behavior is rewarded, wrong behavior is punished. In many individuals this procedure results in the formation of definite habits. The individual acts correctly without thinking about it and without questioning the correctness of his actions. We may therefore tentatively assume that this habitual social behavior is mediated through an appropriate "subcortical" circuit.

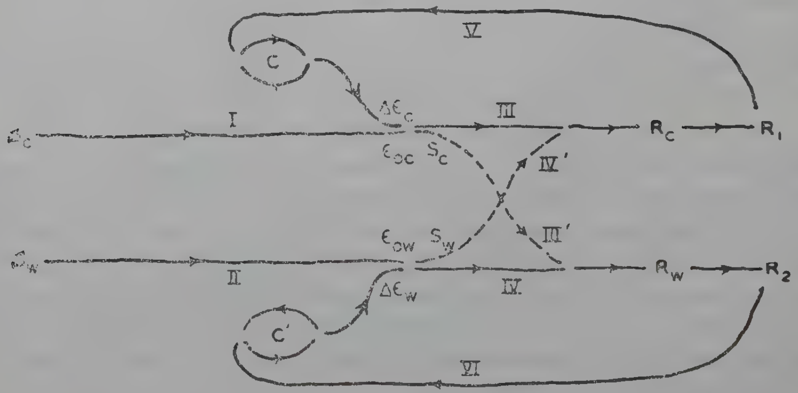

FIGURE 1

Let us now consider the case in which the "incorrect" actions are mediated through a "cortical" circuit and are coincident with a rational discussion of the situation and with a logical analysis of it, which may lead to doubt as to the appropriateness of the socially accepted "correct" reaction. This is not the only possible case, and it must be kept in mind that a number of socially incorrect reactions may be mediated through some other "subcortical" circuit, and not be associated with any particular reasoning. Since, however, the former case is interesting for our problem, we shall consider it in this paper, without prejudice to other possible cases.

Let us therefore assume that a "wrong" reaction not only results in a punishment, but also puts a mechanism for rational thinking into operation, as described elsewhere (Rashevsky, 1948b, chap. xlii), this mechanism making a *rational* choice of a reaction which may be logically preferable to the accepted one.

Schematically the relation between the "subcortical" and the "cortical" circuits is shown in Figure 1, taken from our book (Rashevsky, 1948b, chap. xli). The theory of this neural net, developed by H. D. Landahl, and given in *loc. cit.*, can be used here for our purposes without much change. We presuppose the reader's familiarity with the above-mentioned chapter.

We shall, however, generalize the considerations given in *loc. cit.* by considering not only the probability of "correct" and "wrong" reactions, but also the probability of "no reaction." In other words, we assume that the threshold h of the reciprocal inhibition circuit contained in the network shown in Figure 1 is not negligible (Rashevsky, 1948b, chap. xxxiv). This in its turn means that the difference between the stimuli S_c and S_w, or between the urges to act correctly or wrongly, must be sufficiently large in order to produce any action at all. Otherwise the individual remains undecided.

By evaluating explicitly expression (7) of chapter xxxiv of *loc. cit.*, we find for $h > 0$, and $\varepsilon_c > \varepsilon_w$

$$P_w = \tfrac{1}{2} e^{-k(\varepsilon_c - \varepsilon_w + h)}, \tag{1}$$

which reduces to expression (6) of chapter xli of *loc. cit.* for $h = 0$.

Repeating now the argument of that chapter but using expression (1) above instead of the old one, keeping the same notations and putting $\varepsilon_{0c} - \varepsilon_{0w} = 0$, we arrive at the following expression for the number w of errors as a function of the number n of trials

$$w = -\frac{1}{k(b-\beta)} \log \left[1 + \frac{b-\beta}{2b} e^{-kh} (e^{-kbn} - 1) \right], \tag{2}$$

which for $h = 0$ reduces to equation (7) of chapter xli of *loc. cit.*, if we put $\varepsilon_{0c} - \varepsilon_{0w} = 0$ in the latter.

Let ε_c represent the amount of excitatory factor at the connection s_c, which corresponds to the stimulus, or urge to do as required by the accepted social standards without questioning. Let ε_w denote the amount of excitatory factor at s_w which corresponds to the intensity of stimulation of the "cortical" circuit, which, when set in action, *tries out* on the covert level various other behaviors which are at variance with the accepted one. When this circuit n is in operation, the individual does not uncritically accept the pattern taught to him, but subjects everything to a critical rational analysis. The threshold h is now a characteristic of the two parallel circuits, the "cortical" and the "subcortical." The number n of trials may be considered as proportional to the age T of the individual. Thus, with α as a coefficient, we have

$$n = \alpha T . \tag{3}$$

Introducing this into (2), and putting

$$k\alpha = \gamma , \tag{4}$$

we now obtain

$$w(T) = -\frac{1}{k(b-\beta)} \log \left[1 - \frac{b-\beta}{2b} e^{-kh} (1 - e^{-\gamma b T}) \right] . \tag{5}$$

Equation (5) gives the total number of errors committed by an individual of age T.

As we said above, every time an error is made a set of "mental" trials begins until the individual reasons out a solution which is preferable to the accepted one (Rashevsky, 1948b, chapter xlii). An individual who is not capable of such a reasoning, but accepts without question the behavior taught to him, will never contribute to any changes in the accepted behavior patterns. A society composed of such individuals would never change. On the other hand, individuals who question the existing and accepted behavior patterns, and who are capable of rationally figuring out possible changes in those patterns, will eventually cause a change in at least some of them. For convenience we shall denote an individual who always behaves according to accepted patterns as conservative. An individual who *rationally* behaves differently from the accepted standards we shall call progressive. Care must be taken not to ascribe to the above words their usual rather specific political connotations.

Let the most probable number of "covert trials" required by a given individual to reach a rational solution of the problem be m. The number $1/m$ may be considered as a measure of the individual's reasoning ability. The quantity dw/dT may be considered as a measure of the individual's conservatism.

The "covert" or "mental" trials should not be confused with the "overt" trials, the number of which is defined by (3).

If on the occasion of each wrong reaction one "mental trial" is made, the most probable number of wrong reactions which is required to make the individual find a rational solution is m. Considering the rather natural case in which such an individual, once having found a rational solution, henceforth behaves according to that solution, we find that the probability of an individual to begin to behave in this "progressive" manner at the age T is equal to

$$p = \frac{w(T)}{m}. \tag{6}$$

Equation (6) shows that p increases with reasoning ability.

Equation (5) shows that w increases with T, tending asymptotically to a constant, $w(\infty)$. Hence at any finite time

$$w(T) < w(\infty). \tag{7}$$

Therefore the condition

$$w(\infty) << m \tag{8}$$

will assure a very small probability of an individual becoming spontaneously progressive.

The constant b in equation (5) represents a measure of the social reward for a correct action, the constant β similarly represents a measure of the social punishment for a wrong action.

The reward which an individual receives is in general a function of his socio-economic status. When two individuals are behaving "correctly" in a society in which economic criteria play an important part, the one with the higher socio-economic status is likely to be better rewarded. Therefore it is interesting to consider the case in which b is an increasing function of the income i,

$$b = f(i).$$

We may take, for example,

$$b = \kappa i \qquad \text{or} \qquad b = A \log(1 + i). \tag{9}$$

Similarly β may be a function of i. Most likely β decreases with i. For simplicity we shall limit ourselves to the case where β is constant.

As seen from equation (5) an individual with a larger b, that is, in the upper income bracket, will learn the accepted behavior more rapidly, and also his $w(\infty)$ will be smaller. Hence, *on the average,* individuals in the upper classes are more conservative.

Let an individual of age T have $w(T) << m$, and thus probably be naturally conservative. At that age the values of ε_c and ε_w

are given [Rashevsky, 1948b, chap. xli, equations (4) and (5)] by

$$\varepsilon_c = \varepsilon_{0c} + bc; \qquad \varepsilon_w = \varepsilon_{0w} - \beta w\,. \tag{10}$$

Since $c + w = n$, we have, because of (3),

$$c + w = \alpha T; \qquad c = \alpha T - w\,. \tag{11}$$

Equations (10) and (11) give

$$\varepsilon_c = \varepsilon_{0c} + b\alpha T - bw(T)\,; \qquad \varepsilon_w = \varepsilon_{0w} - \beta w(T)\,. \tag{12}$$

Because of the assumption made originally that $\varepsilon_{0c} = \varepsilon_{0w}$, we find

$$\varepsilon_c - \varepsilon_w = b\alpha T + (\beta - b)\,w(T)\,. \tag{13}$$

Now consider the case in which another individual, or a group of individuals, tries to influence the given individual to behave contrary to the accepted patterns. Formally this will have the same effect as the addition of a positive amount ϕ to the quantity ε_w.

In order for the influence to be effective, that is, in order that the given individual begins to behave contrary to the accepted pattern in a sufficiently large percentage of cases, we must have

$$\varepsilon_w + \phi - \varepsilon_c >> h\,. \tag{14}$$

Let the individual be under this influence of others for a time τ. The probability of a "correct" behavior, while under such influence is given, for $\varepsilon_w > \varepsilon_c$, by

$$Pc' = \tfrac{1}{2}\, e^{-k(h+\varepsilon_w+\phi-\varepsilon_c)}, \tag{15}$$

which, if (14) holds, may be approximately written

$$Pc' = \tfrac{1}{2}\, e^{-k(\varepsilon_w+\phi-\varepsilon_c)}. \tag{16}$$

Hence the approximate probability of a wrong reaction is

$$P_w' = 1 - \tfrac{1}{2}\, e^{-k(\varepsilon_w+\phi-\varepsilon_c)}. \tag{17}$$

When ϕ is very large, or the influence is very strong, P_w' is close to one.

When (14) does not hold there is an appreciable probability of "no reaction" (Rashevsky, 1948b, chap. xxxiv). This may be interpreted as a sort of passive, inertial resistance to any social change without active defense of the existing situation.

During the time τ, the individual makes, according to (3), $\alpha\tau$ trials, and therefore on the average

$$\alpha\tau P_w' = \alpha\tau\,[1 - \tfrac{1}{2}\, e^{-k(\varepsilon_w+\phi-\varepsilon_c)}] \tag{18}$$

wrong reactions. If it takes m wrong reactions to reason out a socially different behavior, then, in order to make the probability of a permanent change to progressive behavior close to one, we must have

$$\alpha_\tau \left[1 - \tfrac{1}{2}\, e^{-k(\varepsilon_w+\phi-\varepsilon_c)}\right] > m \, . \tag{19}$$

From (19) we also have

$$\phi > -\frac{1}{k} \log 2\left(1 - \frac{m}{\alpha_\tau}\right) + (\varepsilon_c - \varepsilon_w) \, . \tag{20}$$

Since $\varepsilon_c - \varepsilon_w$ is given as a function of the age T by equation (13), equation (20) gives us the minimum influence necessary to "convert" an individual of age T to a progressive behavior. We see that ϕ increases with age. Since the expression in brackets of (19) is less than one, $m/\alpha_\tau < 1$. Hence expression (20) shows that ϕ increases with m and decreases with τ.

These considerations could be generalized to the case in which the influence is exerted in "installments," τ_i, so that $\tau = \sum \tau_i$, introducing possible effects of forgetting. If the exact expression (15) is used instead of (16), h will enter into inequality (20). This case may be of special interest. A further generalization to be considered is that of r different possible patterns, in line with H. D. Landahl's theory of learning, to choose from any number of possibilities (Rashevsky, 1948b, chap. xli).

Let the number of individuals at a time t whose age lies between T and $T + dt$ be $N(T, t)\,dT$. At the time $t + \Delta t$ the number of individuals who are of age $T - \Delta t$ at t, will have an age T. Hence, neglecting higher powers of Δ

$$N(T, t + \Delta t) = N(T - \Delta t, t) = N(T, t) - \frac{\partial N(T, t)}{\partial T} \Delta t. \tag{21}$$

This will be the case in the absence of mortality. Actually of the $N(T - \Delta t, t)$ individuals not all will reach the age T, but only the fraction

$$1 - w(T - \Delta t)\,\Delta t \, , \tag{22}$$

or

$$1 - w(T)\,\Delta t + \frac{\partial w}{\partial T} (\Delta t)^2 , \tag{23}$$

where $w(T)$ is the death rate at the age T.

Hence neglecting higher order infinitesimals we find instead of (21)

$$N(T, t+\Delta t) = \left[1 - w(T)\Delta t\right]\left[N(T, t) - \frac{\partial N}{\partial T}\Delta t\right], \qquad (24)$$

or

$$N(T, t+\Delta t) = N(T, t) - \frac{\partial N}{\partial T}\Delta t - w(T)N(T, t)\Delta t. \qquad (25)$$

Hence

$$\Delta N = N(T, t+\Delta t) - N(T, t) = -\frac{\partial N}{\partial T}\Delta t - w(T)N(T, t)\Delta t. \qquad (26)$$

Therefore

$$\frac{\partial N}{\partial t} = -\frac{\partial N}{\partial T} - w(T)N. \qquad (27)$$

This equation gives the variation of $N(T)$ with time. If $\rho(t)$ denotes the total birth rate, which as a rough approximation may be considered as proportional to the whole population

$$\mathfrak{N}(t) = \int_0^\infty N(T, t)\,dT,$$

then we have by a similar argument

$$\rho\mathfrak{N} = \left(\frac{\partial N}{\partial T}\right)_{T=0}. \qquad (28)$$

Of the $N(T)dT$ individuals of age T, $T+dT$, let the number $\theta(T)N(T)dT$ be conservative. Each of those makes

$$\frac{dw(T)}{dT}dt \qquad (29)$$

errors per time dt, where $w(T)$ is given by equation (5). Because of (6), the total loss of conservatives during the time dt is

$$\frac{\theta(T)N(T)dT}{m}\,\frac{dw(T)}{dt}\,dt. \qquad (30)$$

This loss is due to "spontaneous" changes of individuals.

For the probability of a change due to the influence of others we have from (17), putting $\varepsilon_c - \varepsilon_w = \Delta$,

$$\frac{\alpha dT}{m}\left[1 - \tfrac{1}{2}e^{-k(\phi-\Delta)}\right]; \qquad (31)$$

and therefore for the loss in the number of conservatives due to progressive influence, we have

$$\frac{\alpha\theta(T)N(T)dT}{m}\left[1-\tfrac{1}{2}e^{-k(\phi-\Delta)}\right]. \tag{32}$$

The total number of individuals who change during the time *dt* from conservative to progressive is given by the sum of (30) and (32). Therefore

$$\begin{aligned}\frac{\partial}{\partial t}\left[\theta(T)N(T,t)\right] = &-\frac{\theta(T)N(T,t)}{m}\frac{dw_0(T)}{dT}\\ &-\frac{\alpha\theta(T)N(T,t)}{m}\left[1-\tfrac{1}{2}e^{-k(\phi-\Delta)}\right].\end{aligned} \tag{33}$$

The quantity ϕ is given by

$$\phi(t) = \int_0^\infty \theta(T)N(T,t)dT. \tag{34}$$

Substituting (34) into (33), we obtain a very unwieldy nonlinear integrodifferential equation, the discussion of which will be postponed until some future time.

LITERATURE

Householder, A. S. and Landahl, H. D. 1945. *Mathematical Biophysics of the Central Nervous System.* Bloomington, Indiana: The Principia Press.

Rashevsky, N. 1948a. *Mathematical Theory of Human Relations.* Bloomington, Indiana: The Principia Press.

Rashevsky, N. 1948b. *Mathematical Biophysics.* Second Edition. Chicago: The University of Chicago Press.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 11, 1949

TISSUE GROWTH AND CANCER

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Food and metabolic waste products, insofar as they act upon the hereditary substrate of cells, are the most important factors governing tissue growth. Equations describing the growth of tissues are derived in consideration of this fact. A quantity is found in these equations which, if slightly changed, results in very great changes in the growth rate of the tissue, where such very great changes are interpretable as neoplastic growth. The relationship between our equations and similar equations which others have proposed is discussed.

A tissue will be defined as a group of specialized cells differing in structure from other such groups in the adult body (Smith and Copenhaver, 1948). Our objective here is the derivation of growth equations for such tissues. Quantities in these equations will be sought which, if slightly changed, would result in very great changes in the number of cells in the tissue under discussion. These very great changes would be interpretable as neoplastic growth. The search for such quantities has been suggested by N. C. Wetzel (1944) when he mentions that abnormal growth can of itself be due to nothing more than a pathological change in one or more of the same dynamic properties which govern the intricate transactions connected with and leading to the complete and final development of the organism.

Preliminarily heredity as far as it affects growth rate in the tissue will be regarded as a factor of constant magnitude. H. J. Muller (1947) states that, as a result of mitotic divisions, every cell of the developed individual, barring occasional accidents, will come to contain every gene that was present in the original fertilized egg. Likewise, determination will be regarded as complete in the typical tissue under discussion. By determination (Needham, 1942) we mean the fixation of the fate of a part of an organism so that—if it develops further—it will perform one kind of morphogenesis or histogenesis, and one kind only, irrespective of the situation in which it may find itself. The values of the constants in the equations will be taken to represent the genetic make-up of the constituent cells as well as the course of their determination. Hormonal influences will be adjudged, in a sense, to alter heredity, to act in the same way as it does, or to do both. N. C. Wetzel (1944) and M. F. Morales and F. L. Kreutzer (1945) suggest that the effect of hormones on growth may be expressed by changing the values of certain coefficients or constants in the applied growth equations.

The variable by which growth will be represented is cell number. This is used particularly since, in the type of growth known by the pathologist as neoplastic, the one measure of the vastly increased growth activity is the tremendously increased number of cells in some tissue. R. A. Willis (1948) defines a tumor as "an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after cessation of the stimuli which evoked the change." He makes it clear that what he refers to as growth implies cell multiplication by cell division.

The mathematical treatment given below will divide tissues into two groups, each of which will be discussed as a separate case. According to P. E. Smith and W. M. Copenhaver (1948), the duration of life of cells shows great variation. The nerve cells become differentiated very early and lose the power of mitosis. This is probably true of some other cells as well, but most of the cells live a much shorter time. There is a constant replacement of dying and dead cells through mitosis of others. Such mitoses are common in the connective tissue cells and especially in the active secretory cells. As far as nerve cells are concerned, they diminish in number with age. Neuronophagia occurs in the cerebral cortex of man and is found most abundant in the senile brain (Andrew and Cardwell, 1940).

Case I will include tissues in which there is a constant replacement of cells throughout the life span of the organism by new cells. Case II will include tissues in which cells, following a short period after birth, no longer multiply, but undergo a gradual decrease in number with the advance of age. For most purposes Case I can readily be said to include those tissues in which cancer occurs significantly and Case II those tissues in which cancer does not occur significantly.

Let $n =$ number of cells in the tissue under discussion, $t =$ time, $dB/dt =$ time rate of formation of new cells, and $dD/dt =$ time rate of death of cells.

Then

$$\frac{dn}{dt} = \frac{dB}{dt} - \frac{dD}{dt}. \tag{1}$$

The term "medium" will be used to refer to the tissue's immediate environment. This environment has been called tissue fluid (Cowdry, 1944). Tissue fluid lies between the extravascular cells throughout the body and the endothelial walls of capillaries. Materials passing from the bloodstream must penetrate through the endothelium and enter the tissue fluid before they reach the cell membrane. The cells derive their nourishment immediately from the tissue fluid, as well as eliminate their wastes into it. Let F = the amount of food in the medium. By food we mean those chemical substances which are taken by the cells from their environment, whether these substances be solid, liquid, or gaseous. Let T = the amount of waste products of metabolism in the medium.

In Case I we assume

$$\frac{1}{n}\frac{dB}{dt}=\frac{a(F-b)}{q+(F-b)}-cT, \tag{2}$$

where a, b, c, and q are positive constants, and with the limitation that

$$\frac{dB}{dt}>0\,. \tag{3}$$

The effect of food on $\frac{1}{n}\frac{dB}{dt}$ in the situation where $T=0$ is analogous to the representation of an adsorption isotherm by

$$\sigma=\frac{b_0c_0}{1+b_0c_0}, \tag{4}$$

where σ = the fraction of surface occupied by adsorbed molecules, c_0 = the concentration of the adsorbable substance in the adjoining gas or solution, and b_0 is a constant (Hinshelwood, 1946). When c_0 is small in equation (4), σ is approximately in direct proportion to it, and when c_0 is large, σ is almost independent of c_0. The same is true of the relation of $(F-b)$ to the quantity

$$a(F-b)/[q+(F-b)]\,.$$

It is to be noted that the use of b in equation (2) makes the presence of a certain minimum amount of F (equal to b) necessary in the medium before any cell division can occur, even when the amount of T present is zero. The explanation of the above-mentioned dependence of $\frac{1}{n}\frac{dB}{dt}$ on F may not, however, be based entirely, or even significantly, on adsorption processes. N. Rashevsky (1938) shows through a mathematical treatment that, while down to a certain concentration of oxygen the rate of oxygen consumption of a cell remains constant, below the critical point the rate of consumption falls to zero with decreasing oxygen concentration. His discussion shows that an incomplete penetration of oxygen into the cell may be the cause of this effect. His arguments apply just as well to other diffusable substances in the medium. The experimental work of W. Kempner (1936) shows that one must go down to very low oxygen tensions before the decrease of respiration at such tensions may be perceived. He also showed (1937) that the growth of aerobic bacteria is inhibited by lowered oxygen tension. As far as the cT term in equation (2) is concerned, we might say that T will affect growth in lower quantities than are necessary to affect other cell functions. M. Rubner (1924), by placing yeast cells in different concentrations of salt, reduced their water content and—when the concentration was sufficiently raised—their heat production. But only a mild degree of hypertony was required to stop growth. It is to be realized that the values for such constants as a, b, c, and q will be different in different tissues. Letting F get very large and letting T become insignificantly small gives us optimum conditions for cell multiplication with $\frac{1}{n}\frac{dB}{dt}$ equal to the constant a. A. Fisher (1946) says that cells proliferate at a very definite rate which is characteristic of the particular cell type and which is in fixed ratio to the rate of proliferation of other types, and that differences in the duration of the interkinesis may be imagined to be the primary cause of organization and differentiation. Expressing the same concept in a somewhat different way, J. Needham (1942) mentions that a specific rate of relative growth, expressible by a heterauxetic constant, may be regarded as the fate of an organ, permitting us to speak of the determination of a growth rate.

Assume

$$\frac{1}{n}\frac{dD}{dt}=pT, \tag{5}$$

which is almost the simplest way in which $\frac{1}{n}\frac{dD}{dt}$ could be made dependent upon T.

It is to be especially noted that through equations (5), (2), and (1), $\frac{1}{n}\frac{dn}{dt}$ is a function of F and T only. These two factors are probably the two most important ones affecting growth rate. A. Fisher (1946) states that the primary cause of the aging of cells is not to be found in the cells themselves, since senility and death are due to external factors, i.e., accumulation of metabolic products and lack of nutrient substance. E. B. Wilson (1925) explains modern ideas of senescence to emphasize the importance of the accumulation of relatively inactive products. According to C. C. Little (1947), when waste material is promptly and completely removed and when a steady and adequate supply of food is provided, growth is continuous and shows no sign of slowing down. C. M. Child (1923) gives the general result of the aging process as a decrease in the metabolic activity of each unit of the organism because the proportion of the relatively stable constituents in the living substratum increases. J. Needham (1942) refers to the declining basal metabolic rate with advancing age as due to the changing relative proportion of respiring protoplasm and inert material in the cells.

In our present theory specific growth-promoting substances in the medium are not considered, except insofar as they might be accounted for as part of the constituents of F. A. Fisher (1946, p. 250) says: " . . . . age brings about certain changes in the serum reflected in the rate of growth of tissue cells cultivated therein. The changes are characterized by an increase in the amount of growth-inhibiting, and not by a loss of growth-promoting factors." The effect of growth-promoting substances may not be important in the intact organism's tissues, since these substances are produced by the breakdown of leucocytes, and this may not occur to any appreciable extent in the vicinity of most types of tissue cells. Nevertheless, it may well be that a more adequate mathematical treatment will necessitate their consideration. A. Carrel and A. H. Ebeling (1923) mention the increased restraining effect of serum on growth in old age as being due, at least in part, to an increased amount of inhibiting principles.

For our purposes it will be convenient to classify intracellular biochemical (or metabolic) reactions into two groups: (1) maintenance reactions, which are necessary to maintain the cell protoplasm in its living state; (2) growth reactions, which increase the amount of protoplasm in cells. Whether an organism grows or not, it must obtain energy for the process of living, and this energy is obtained from oxidative processes; some food materials are built up into protoplasm, while others are utilized to produce energy by their oxidation (Heilbrunn, 1943). J. Needham (1942) mentions that there are certain cases in which it has been shown that metabolism can occur in the absence of growth so that cell division is quite absent and the cells are simply maintaining themselves as far as possible in the status quo. The differences between the dietary requirements of amino acids for growth and for the maintenance of nitrogen equilibrium (Burroughs, Burroughs, and Mitchell, 1940) emphasize the same concept. The rate of maintenance metabolism will be assumed proportional to the number of living cells present in the tissue, while the growth metabolism can be considered proportional to the birth rate of new cells. In justification of this assumption, we mention that during the lifetime of a tissue region the cells remain within the same average order of magnitude as far as their size is concerned.

We will assume that the vascular bed of the tissue region grows in direct proportion to the tissue region itself, whether that growth is of a positive or negative type. In experimental work done on the skin (Weiss and Frazier, 1930), it was found that the radius of the cell area supplied by a single surface capillary might be the same in an aged individual as that in a young adult, and that reduction in the number of capillaries cannot be held responsible for the changes observed with advancing age. As a consequence the ability of the blood vessels in a tissue to supply it with food or remove its wastes should be proportional to the number of cells in the tissue.

In consideration of the foregoing discussion we set down the following equation:

$$-\frac{1}{n}\frac{dF}{dt}=d+\frac{f}{n}\frac{dB}{dt}-g, \tag{6}$$

where d, f, and g are positive constants. We let $d =$ the amount of F used up for maintenance metabolism by a cell in a unit time, $g =$ the amount of F supplied by the vascular bed of the tissue to a single cell in a unit time, and $f =$ the amount of F used up in growth metabolism leading to the addition of another cell to the tissue region.

With the exception of one additional term, the expression used to describe the change in T follows the same form as does that for F, so that we have

$$\frac{1}{n}\frac{dT}{dt}=h+\frac{i}{n}\frac{dB}{dt}+\frac{j}{n}\frac{dD}{dt}-m, \tag{7}$$

where h, i, j, and m are positive constants to be defined below. The $\frac{j}{n}\frac{dD}{dt}$ term accounts for waste products yielded up into the medium when a cell dies there. Now in equation (7) we will let $h =$ the amount of T from the maintenance metabolism of a single cell produced in a unit time, $i =$ the amount of T produced by that quantity of growth metabolism leading to the addition of another cell to the tissue region, $j =$ the amount of T produced by the death of a single cell in the tissue region, and $m =$ the amount of T removed by the vascular bed of the tissue from a single cell in a unit time.

In Case II we assume

$$\frac{dB}{dt} = 0 \tag{8}$$

at all times. From equation (1)

$$\frac{1}{n}\frac{dn}{dt} = -\frac{1}{n}\frac{dD}{dt}. \tag{9}$$

Reasoning as in equations (2) and (5)

$$\frac{1}{n}\frac{dD}{dt} = p''T - \frac{a'(F-b')}{q' + (F-b')}, \tag{10}$$

with p'', a', q', and b' positive constants. In examining (10) it will be noted that a certain part of the death rate will be due to starvation (or lack of F). In equation (2), which belongs to Case I, food deficiency lowers the birth rate, but does not affect the death rate. Equation (6) becomes for this case

$$-\frac{1}{n}\frac{dF}{dt} = d' - g'. \tag{11}$$

Equation (7) becomes

$$\frac{1}{n}\frac{dT}{dt} = h' + \frac{j'}{n}\frac{dD}{dt} - m', \tag{12}$$

with d', g', h', j', and m' positive constants. This completes our discussion of Case II for the present.

In expression (2) $\frac{1}{n}\frac{dB}{dt}$ was made dependent on F, letting what we have called growth metabolism be a function of F. On the other hand in equations (6) and (7) we have used the constants d and h to represent maintenance metabolism independent of F. This is justified at least in Case I since in that case there is cell replacement all through life indicating that there is adequate F present to do so. There is considerable likelihood that, when available food is lessened, growth metabolism may decrease and disappear though for a long time maintenance metabolism will continue, with a much lower level of F required to make maintenance metabolism dependent on F than to make growth metabolism so dependent. Pertinent to this, A. G. Hogan and R. W. Pilcher (1933) showed in mammalian experiments that the basal metabolism of their animals was apparently the same regardless of the amount of protein consumed, but that the high protein groups grew more rapidly than those on low protein rations.

Case I is certainly the more important case for our study since among the tissues included within its range of description occur the vast majority of cancers. Summarizing Case I we list the following set of simultaneous differential equations.

$$\left\{\begin{aligned}
&\frac{dn}{dt}=\frac{dB}{dt}-\frac{dD}{dt};\\
&\frac{1}{n}\frac{dB}{dt}=\frac{a(F-b)}{q+(F-b)}-cT; \qquad \left(\frac{dB}{dt}>0\right);\\
&\frac{1}{n}\frac{dD}{dt}=pT;\\
&-\frac{1}{n}\frac{dF}{dt}=d+\frac{f}{n}\frac{dB}{dt}-g;\\
&\frac{1}{n}\frac{dT}{dt}=h+\frac{i}{n}\frac{dB}{dt}+\frac{j}{n}\frac{dD}{dt}-m.
\end{aligned}\right.$$

It may be said parenthetically that the relation between the number of cells in a tissue and the weight of that tissue may be given by the following equation

$$\frac{dw}{dt}=v\frac{dn}{dt}+z\frac{dT}{dt}, \qquad (13)$$

where $w=$ the weight of a tissue, and where v and z are constant coefficients.

Putting equations (2) and (5) into (1) we have

$$\frac{1}{n}\frac{dn}{dt}=\frac{a(F-b)}{q+(F-b)}-cT-pT. \qquad (14)$$

Using equation (2) in (6) we have

$$-\frac{1}{n}\frac{dF}{dt}=d+f\left[\frac{a(F-b)}{q+(F-b)}-cT\right]-g. \qquad (15)$$

Using equations (2) and (5) in (7) we have

$$\frac{1}{n}\frac{dT}{dt} = h + i\left[\frac{a(F-b)}{q+(F-b)} - cT\right] + jpT - m. \tag{16}$$

As is justified in our discussion about (2) we can let

$$\frac{a(F-b)}{q+(F-b)} \simeq a \tag{17}$$

when F is large, but when F is small we let

$$\frac{a(F-b)}{q+(F-b)} \simeq \frac{a(F-b)}{q}. \tag{18}$$

In this sense a large F is greater than $q+b$ while a small F is smaller than $q+b$.

Because of the mathematical difficulty inherent in the solution of equations such as (14), (15), and (16), we will use the approximations (17) and (18). First we shall apply (17). Then from equations (14) and (16) we have

$$\frac{1}{n}\frac{dn}{dt} = a - (c+p)T\,; \tag{19}$$

$$\frac{1}{n}\frac{dT}{dt} = h - m + ia + (jp - ic)T. \tag{20}$$

Let

$$dx = n\,dt\,. \tag{21}$$

Then

$$\frac{dn}{dx} = a - (c+p)T; \tag{22}$$

$$\frac{dT}{dx} = h - m + ia + (jp - ic)T. \tag{23}$$

Equation (23) has separable variables so that we can solve for T and obtain

$$T = \frac{c'e^{(jp-ic)x}}{jp-ic} - \frac{h+ia-m}{jp-ic}, \tag{24}$$

where c' is an integration constant. When $x=0$, let $T=0$ so that

$$T = \frac{h+ia-m}{jp-ic}\left[e^{(jp-ic)x} - 1\right]. \tag{25}$$

Putting equation (25) into (22) and then solving the resulting equation by separating variables gives

$$n = \left[a + \frac{(c+p)(h+ia-m)}{jp-ic} \right] x - \frac{(c+p)(h+ia-m)}{(jp-ic)^2} e^{(jp-ic)x} + c'' , \tag{26}$$

where c'' is an integration constant. When $x = 0$, $n = n_0$ so that

$$n = \left[a + \frac{(c+p)(h+ia-m)}{jp-ic} \right] x - \frac{(c+p)(h+ia-m)}{(jp-ic)^2} \times \left[e^{(jp-ic)x} - 1 \right] + n_0 ; \tag{27}$$

$$t = \int_0^x \frac{dx}{n(x)} ; \tag{28}$$

constituting the solution of equations (19) and (20).

Concerning the biological meaning of x, it seems best to consider it as a kind of biological time or at least a measure of such. The quantity x is a function of t whose derivative with respect to t is always positive, as is shown in its definition in equation (21), where $n > 0$ in all situations biologically meaningful. The integral

$$\int_0^t ndt$$

has been described as representing a cumulative toxic effect by V. Volterra and U. D'Ancona (1935), V. A. Kostitzin (1939), and C. N. Hinshelwood (1946). This concept is allied with A. Carrel's (1931) discussion of biological time. He explains that physical time ($= t$), which is measured by a clock, differs from the time which we live, and that at all levels of biological organization the cause of duration seems to consist of the modification of their medium produced by living structures, and of the secondary changes undergone by these structures under the influence of the modified medium. The same sort of idea is emphasized in a different manner by F. G. Donnan (1936), when he mentions that for the description of the change of living systems in time a pure differential analysis will not suffice. In such cases one must use instead integro-differential equations giving a

" . . . . mathematical description of a living organism as a special type of world-tube in space-time."

The quantity $jp - ic$ is the difference between two quantities, which are surmised to be of the same order of magnitude. If this supposition is correct, then small changes in jp or ic, or in both, which will permit each to remain of the same order of magnitude as it was previously, will cause relatively much larger changes in the magnitude of $jp - ic$ relative to its original magnitude. Attention is now directed to determining how changes in $jp - ic$ could account for a change of growth from the normal to the neoplastic type. It should be remarked that we certainly do not believe that changes in j, p, i, or c are the only ones which could account for a transformation to cancerous growth. Although we do not engage in a detailed study of them at this time, positive changes in a would seem quite capable of producing neoplastic proliferation.

Taking the derivative of equation (27) we obtain

$$\frac{dn}{dx} = a + \frac{(c+p)(h+ia-m)}{jp-ic}\left[1 - e^{(jp-ic)x}\right]. \tag{29}$$

Setting equation (29) equal to zero and solving for x_{max}, it is found that

$$x_{max} = \frac{1}{jp-ic}\, ln\left[\frac{a(jp-ic)}{(c+p)(h+ia-m)} + 1\right];$$

If $jp - ic$ is less than $-\dfrac{(c+p)(h+ia-m)}{a}$, x_{max} does not exist. In normal growth there is a positive x_{max}, which gives a maximum n. Then normally $jp - ic$ must be greater than

$$-\frac{(c+p)(h+ia-m)}{a}.$$

The condition for the existence of a maximum of n is not only that $dn/dx = 0$ be an equation having a positive root $x = x_{max}$, but also that d^2n/dx^2 be negative for $x = x_{max}$. Taking the derivative of equation (29), we obtain

$$d^2n/dx^2 = -(c+p)(h+ia-m)\,e^{(jp-ic)x}.$$

In order for d^2n/dx^2 in the above equation to be negative for any value of x, $(c+p)(h+ia-m)$ must be positive. Since both c and p must be positive from their biological meanings, then, from the above-mentioned considerations, $(h+ia-m)$ must be a positive quantity in order that normal growth may occur.

We have carried out a graphical integration of the expression whose integral is indicated in equation (28). In order to do this $1/n$ was plotted against x in Figure 1 with $jp - ic$ given different values in each of the figures. (In all the figures the symbol y is to be taken as having a meaning identical with the expression $jp - ic$.) In Figure 1, when $1/n$ was plotted against x when $jp - ic = 0$, it is noted that an indeterminate expression of the form $0/0$ had to be evaluated, as is obvious from the form of the functional relationship between $jp - ic$ and n given in equation (27). Returning to (23), letting $jp - ic = 0$, integrating the resulting expression, and assuming as before that when $x = 0$, $T = 0$, we have

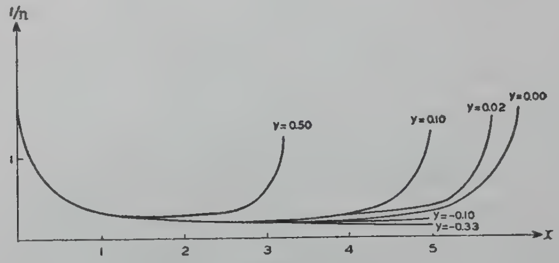

FIGURE 1

$$T = (h - m + ia)x\,.$$

Substituting this result into equation (22) gives

$$dn/dx = a - (c + p)(h + ia - m)x\,,$$

which when integrated with respect to x becomes

$$n = ax - (c + p)(h + ia - m)x^2/2 + n_0\,.$$

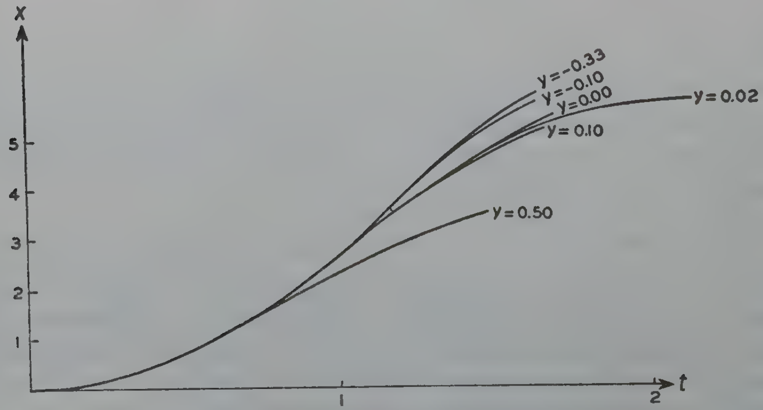

FIGURE 2

This is the equation we have used in plotting the curve in Figure 1. The planimeter was utilized to measure areas under the curves on the graphs enabling us to plot t against x in Figure 2. By using these graphs (Figures 1 and 2), it is possible to find values of n and t corresponding to a given x so that a direct relation between n and t is obtained, with the variable x eliminated. This relation is graphed on Figure 3. In preparing the graphs arbitrary values have been assumed for a and $(c + p)(h + ia - m)$. (In preparing the graphs given here we have used $n = 0.5$, $a = 3$, and $(c + p)(h + ia - m) = 1$.) To obtain actual values for a, $(c + p)(h + ia - m)$, and $jp - ic$ on the basis of available data requires a tedious numerical computation which we have not done at the present time. It should be remembered that the units used in the figures are purely arbitrary.

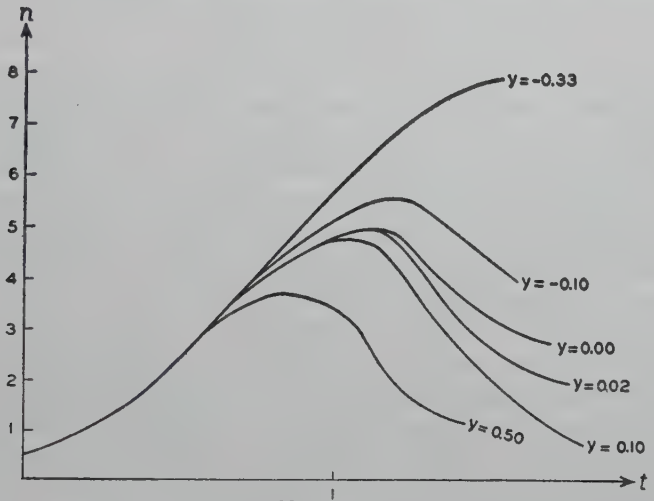

FIGURE 3

From Figure 3 it can be seen that, when

$$jp - ic > -(c + p)(h + ia - m)/a,$$

the resultant curve giving n as a function of t is quite representative of the pattern which normal growth takes. This curve fits well the description of normal growth given by D. W. Thompson (1942). He states that rate of growth, which is represented by the slope of our curves in Figure 3, depends on the age of the organism. It has a maximum early in life, after which epoch of maximum it slowly declines. This means that there is a point of inflection, or abrupt change from an increasing to a decreasing velocity of growth. Negative growth occurs with old age. The marked manner in which growth is affected, in the way of acceleration or retardation, at certain physiological epochs of life, such as birth and puberty, is explicable on the basis of a change in the values of the coefficients due to hormonal influences at the time of puberty and to completion of determination at the period shortly following birth.

It is seen in Figure 3 that a decrease in $jp - ic$ produces an increase in growth rate. If $jp - ic$ is decreased down to

$$-(c+p)(h+ia-m)/a\,,$$

n no longer has a maximum, but approaches an asymptote represented by the line $n = a^2/[(c+p)(h+ia-m)] + n_0$. Though we have not plotted a curve for $jp - ic < -(c+p)(h+ia-m)/a$, a study of equation (29) shows that when much time has elapsed, the $e^{(jp-ic)x}$ term is insignificant and n follows the so-called exponential type of growth, in which dn/dt is equal to some positive constant times n. This curve never has a point of inflection at all.

A small decrease of $jp - ic$ from the normal would cause the new growth curve to reach a maximum larger and later than, but close to, the normal maximum. When the decrease in $jp - ic$ is great, the very large maximum n may never be reached during the life span of the individual, but occurs at the end of a longer time; or, if the decrease in $jp - ic$ is sufficiently great, there will never be a maximum n. The former type of growth may be interpreted as that of a benign tumor and the latter as that of a malignant tumor.

We have already made some mention of the factors determining the magnitudes of our constants. Of these, hormonal and genetic influences are variable in the postnatal lifetime of an organism. As far as endocrinological activity, this is obvious, but genetic factors in somatic cells undoubtedly change as well. Important in this is the influence of stray radiation and the molecular readjustments occurring incident to the thermal agitation present at the temperatures at which life exists (Schrödinger, 1945; Muller, 1947). The concept ennunciated here assumes the existence of somatic mutations, which give rise to changes in the individual body which, of course, cannot be transmitted by the germ cells, but may be perpetuated by vegetative reproduction (Woodruff, 1941). Also causing alterations in the magnitudes of the constants very early in life are the changes leading to the completion of determination. That determination is not complete until some time early in postnatal existence is suggested by the inability of the newly born organism to form antibodies and the correspondence of this inability to the time when antigenic specificity among tissues has not yet developed (Needham, 1942). This situation is significant with regard to the causation of embryonic tumors, in which the disturbed chemistry of the organizers with its consequent effect on the course of determination is most important (Willis, 1948).

When a change in $jp - ic$ occurred, it might be argued that it would take place in only a very few cells in a tissue, while the present theory has been described as giving the behavior of a tissue as a whole, with n being the total number of cells in the tissue. In order to apply the theory to this situation, we might regard $jp - ic$ as an average over the entire tissue, with any change occurring gradually and reaching its final value when the entire tissue is replaced by the cells possessing the changed value of $jp - ic$. An alternative would be to use a different n in this situation, where the n would not be the total number of cells in the particular tissue, but would be the number of those cells with the altered value for $jp - ic$. Here again, as the tissues were replaced by neoplastic (having the lowered value of $jp - ic$) cells, this n would become identical with the n described in the general definition of n mentioned earlier.

Without further study it might seem obscure just how the previously mentioned changes in such constants as j, p, i, and c could result in sudden increases in growth rates. Remembering equations (2), (5), (7), (17), (21), and (25) we obtain

$$dT/dx = (h + ia - m)\, e^{(jp-ic)x}\,; \tag{30}$$

$$dD/dx = p[(h + ia - m)/(jp - ic)]\,[e^{(jp-ic)x} - 1]\,; \tag{31}$$

$$dB/dx = a - c[(h + ia - m)/(jp - ic)]\,[e^{(jp-ic)x} - 1]. \tag{32}$$

No matter how big or how small $jp - ic$ may be, dT/dt is always positive. A positive $jp - ic$ will cause d^2T/dx^2 to be positive, while a negative $jp - ic$ will cause d^2T/dx^2 to be negative, with dT/dx approaching zero as t increases. No matter what the magnitude of $jp - ic$ may be, dD/dt is always positive. When $jp - ic > 0$, $d^2D/dx^2 > 0$; when $jp - ic < 0$, $d^2D/dx^2 < 0$ with dD/dx approaching a constant value $- p(h + ia - m)/(jp - ic)$ as t increases. When $jp - ic > 0$, dB/dt can become negative when t is great enough. This is prohibited by the limitation imposed in equation (3). In order to take care of this difficulty, we must put a limit on the size which a positive $jp - ic$ may possess. Considering the fact that x reaches a maximum when n has come down to a zero value at some late time and remembering equation (27), it is evident that this maximum permissible value for $jp - ic$ is then the proper positive solution of the following simultaneous set for $(jp - ic)_m$.

$$c[(h + ia - m)/(jp - ic)_m]\,[e^{(jp-ic)_m x_m} - 1] = a\,, \tag{33}$$

$$\begin{aligned}&[a + (c + p)(h + ia - m)/(jp - ic)_m]x_m\\&\quad - [(c + p)(h + ia - m)/(jp - ic)_m{}^2]\,[e^{(jp-ic)_m x_m} - 1] + n_0 = 0\,.\end{aligned} \tag{34}$$

Equation (32) further shows that the inhibition to cell birth (or cell division) per cell by T approaches a constant limiting value $c(h + ia - m)/(jp - ic)$ when $jp - ic < 0$ as t gets greater. An examination of equation (32) shows that there is a minimum value down to which $jp - ic$ can go without making $dB/dt < 0$, depending on the maximum size which x can eventually reach. This size of x is a solution of equation (34) for x_m. This minimum value for $jp - ic$ will be obtained as a negative root of (33) when it is solved after the proper solution of (34) for x_m has been substituted into it.

Using equations (29) and (1) we have

$$\begin{aligned}dn/dx &= dB/dx - dD/dx\\&= a - [(c + p)(h + ia - m)/(jp - ic)]\,[e^{(jp-ic)x} - 1]\\&= a + (c + p)(h + ia - m)/(jp - ic)\\&\quad - [(c + p)(h + ia - m)/(jp - ic)]\,[e^{(jp-ic)x}]\,.\end{aligned} \tag{35}$$

From the above manner of expressing dn/dx, it can be seen why, when $jp - ic$ becomes less than a certain minimum value $-(c + p)(h + ia - m)/a$, dn/dt never becomes negative. When x is large, $-[(c + p)(h + ia - m)/(jp - ic)]\,e^{(jp-ic)x}$ becomes insignificant, provided $jp - ic$ is negative. If $jp - ic > -(c + p)(h + ia - m)/a$ but is still negative, then $a + (c + p)(h + ia - m)/(jp - ic) < 0$ and so causes dn/dt to become negative when t is great. However, when $jp - ic < -(c + p)(h + ia - m)/a$, $a + (c + p)(h + ia - m)/(jp - ic)$ is positive and so when t is great and $-[(c + p)(h + ia - m)/(jp - ic)]\,e^{(jp-ic)x}$ is very small, dn/dt is still positive. It is, of course, quite evident that as long as $jp - ic < 0$, $-[(c + p)(h + ia - m)/(jp - ic)]\,e^{(jp-ic)x}$ is a positive quantity.

Taking the derivative of equation (19) with respect to x gives

$$d^2n/dx^2 = -(c + p)\,dT/dx\,. \tag{36}$$

Using equation (23) in (36) we have

$$d^2n/dx^2 = -(c + p)\,[h + ia - m + (jp - ic)T]\,. \tag{37}$$

Solving equation (19) for T and putting this expression into (37), we get

$$\begin{aligned}d^2n/dx^2 &= -(c + p)\,[h - m + ia\\&\qquad + (jp - ic)(a - dn/dx)/(c + p)]\,.\end{aligned} \tag{38}$$

Integrating (38) with respect to x and remembering that when $T = 0$, $dn/dx = a$, and using (21), we obtain the following:

$$dn/dt = [a - n_0(jp - ic)]\,n - (ic - jp)\,n^2 - \{(c + p)(h - m + ia) + a(jp - ic)\}\,n \int_0^t n\,dt. \tag{39}$$

When

$$jp - ic = -(c + p)(h - m + ia)/a, \tag{40}$$

$$dn/dt = [a - n_0(jp - ic)]\,n - (ic - jp)\,n^2. \tag{41}$$

Equation (41) represents the logistic curve. A large amount of statistical and experimental study has shown that populations of the most diverse kinds are found statistically to follow in their growth a particular type of curve, the logistic (Pearl, 1927).

A rationalization of the logistic curve was made by A. J. Lotka (1925) in the following way. He assumed that

$$dX/dt = F(X), \tag{42}$$

where X was the mass of the system. The equation $F(X) = 0$ has a root at $X = 0$, for at least one individual is required to start the growth of a population. Expanding by MacLaurin's formula, there will be a series for F lacking the constant term. Thus

$$dX/dt = F(X) = aX + bX^2 + cX^3 \cdots. \tag{43}$$

Furthermore, equation (43) should have at least one other root, since there must be some upper limit to the growth of the population. The simplest case satisfying this condition is that in which the right-hand member of (43) terminates at the second degree term, i.e.,

$$dX/dt = aX + bX^2. \tag{44}$$

V. A. Kostitzin (1939) derives the logistic curve from somewhat different considerations. He assumes that†

$$\text{Number of births in } (t, t + h^*) \simeq Np^*h^*,$$

$$\text{Number of deaths in } (t, t + h^*) \simeq Mp^*h^*,$$

where he calls N and M uncorrected coefficients of birth rate and mortality, and where p^* is the population. From this we get

$$p^*(t + h) - p^*(t) = Np^*h^* - Mp^*h^*.$$

Dividing by h^* and proceeding to the limit as h^* approaches zero, we get

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†Asterisks are used after all of Kostitzin's symbols which might be confused with our symbols.

$$p^{*\prime}(t) = Np^*(t) - Mp^*(t). \tag{45}$$

The coefficients N and M are not constant but are dependent on p^*. Kostitzin puts this dependence in the following form

$$N = n^* - \nu p^*, \tag{46}$$

$$M = m^* + \mu p^*, \tag{47}$$

where n^*, ν, m^*, and μ are constants. Putting equations (46) and (47) into (45) gives us

$$p^{*\prime}(t) = \varepsilon p^*(t) - hp^{*2}(t), \tag{48}$$

where

$$\varepsilon = n^* - m^*, \tag{49}$$

and

$$h = \nu + \mu. \tag{50}$$

In order to show the equivalence of Kostitzin's work and our own, it is necessary to substitute the following for equations (46) and (47)

$$N = n^* - \nu(p^* - p_0); \tag{51}$$

$$M = m^* + \mu(p^* - p_0); \tag{52}$$

where p_0 is the value of p^* when $t = 0$. Using equations (32) and (51) it becomes evident that by substituting $t = 0$, we obtain

$$n^* = a.$$

By using equations (31) and (51) and letting $t = 0$, it can be seen that

$$m^* = 0.$$

From equations (41), (48), and (50) it follows that

$$h^* = ic - jp = \nu + \mu.$$

If $p = 0$, $dD/dx = 0$ and $\mu = 0$. Then we have shown that

$$\nu = ic.$$

Consequently, when p has a value greater than zero, it must be true that

$$\mu = -jp.$$

Equation (39) is of exactly the same form as the equation proposed by V. Volterra and U. D'Ancona (1935) and solved exactly by V. A. Kostitzin (1939) to give a solution having the same mathematical form as the one we have obtained in (27). The

$$\int_0^t n\,dt$$

in equation (39) is described by Kostitzin as representing a total toxic action on the birth and death rates because of the accumulation of metabolic products. We can place Kostitzin's equations (46) and (47) into our own notation and also show in the more complete case that

$$N = dB/dx = a + icn_0 - icn - c(h-m)\int_0^t n\,dt\,,$$

$$M = dD/dx = jpn_0 - jpn + p(h - m + ia + aj)\int_0^t n\,dt\,.$$

The means by which the coefficients for the

$$\int_0^t n\,dt$$

term were selected become obvious if we assume a zero death rate due to $p = 0$ in equation (39) and then obtain the effect of the

$$\int_0^t n\,dt$$

term on the birth rate.

V. Volterra (1938) proposes the equation†

$$dN/dt = -(c^* - b^*N + a^*N^2)N\,. \tag{53}$$

If we assume as an approximation that

$$dt = r\,dn\,,$$

where r is a constant, and use this approximation to carry out the indicated integration in (39), we have

$$\begin{aligned} dn/dt = {} & [a - n_0(jp - ic)]\,n - (ic - jp)\,n^2 \\ & - \{(c + p)(h - m + ia) + a(jp - ic)\}\,r(n^3 - n_0^3)/2\,, \end{aligned}$$

which is of the same form as Volterra's equation.

In a previous paper (Kesselman, 1948), we proposed a growth equation. The G_i used there is equivalent to a in the present treatment, while the J_i is the equivalent of $nT(c + p)$. The discussion of the nature of the action of carcinogenic agencies given there, which stresses the importance of the relative magnitudes of N_iG_i and J_i, is just as applicable to the present theory.

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†Asterisks are used after all of Volterra's symbols which might be confused with our symbols.

If we assume that neoplastic growth signifies an increase of dn/dt above the normal value, Figure 3 shows that two tissues of the same histologic type with different values of y may grow at the same rate during early life, but later one of them may change to neoplastic growth, the other maintaining the normal growth pattern. Changes in y occurring later in life must be examined in a different way, since growth curves of tissues with different values of y are then quite individual in character.

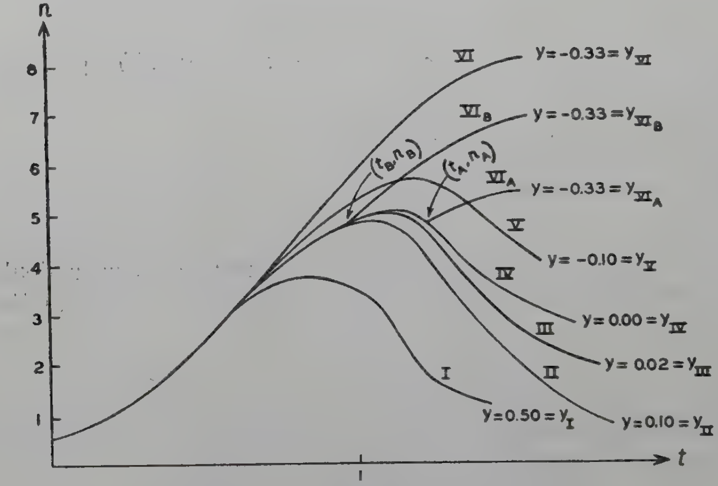

FIGURE 4

Suppose that at time t_A a change in y (see Figure 4) from y_{IV} to y_{VI} (given as y_{VI_A} in Figure 4) occurs in a tissue composed of n_A cells at t_A. Curve VI will not describe the growth of the altered tissue after t_A, since at t_A tissue VI (described by curve VI) will contain a number of cells much greater than n_A. Let us cut away at t_A a portion of tissue VI so that the cells remaining in it are n_A in number. At this time it becomes necessary to realize that in the present study there has been a tacit assumption that the volume occupied by T and F has remained constant in time. This is obvious on examination of equations (2) and (5). In these equations neither $\frac{1}{n}\frac{dB}{dt}$ or $\frac{1}{n}\frac{dD}{dt}$ can depend on total quantities of T or F, but can only be dependent upon concentrations of these materials. Suppose that $n = n_{\mathrm{VI}}$ in equation (14) giving

$$\frac{1}{n_{\mathrm{VI}}}\frac{dn_{\mathrm{VI}}}{dt} = \frac{a(F-b)}{q+(F-b)} - cT - pT.$$

If $1/s$ of n_{VI} is removed from tissue VI, then

$$\frac{1}{n_{\mathrm{VI}}/s}\frac{d(n_{\mathrm{VI}}/s)}{dt} = \frac{a(F-b)}{q+(F-b)} - cT - pT, \tag{54}$$

since this partitioning will not affect the right-hand side of equation (54) at all. It becomes obvious that tissue VI_A has its growth after t_A correctly described by

$$n_{\mathrm{VI}_A} = \frac{1}{s}\int_0^t \left[\frac{a(F-b)}{q+(F-b)} - (c+p)T\right] n_{\mathrm{VI}}dt,$$

where s is the ratio of n_A to the number of cells in tissue VI at t_A, and where the integral expression has already been plotted as curve VI. In Figure 4, n_{VI_A} has been plotted against t.

From the above discussion and an examination of Figure 4, it appears that a decrease of y in early life will not alter dn/dt much, but in later life will have a far more marked effect in doing this. This observation agrees with the observed steep and continuous rise of the incidence of fatal carcinoma in old age (Willis, 1948). The graphs further suggest, in agreement with certain experimental and statistical observations, that cancer is a disease of the elderly, because of the unusually long latent periods elapsing between the application of carcinogenic stimuli and the development of tumors.

Tumors in early life tend to progress more rapidly and disseminate more frequently than do the same tumors in later life (Moore, 1944). This means that in a young person a cancer grows much more rapidly than in an older person. Suppose that tissue IV at $t = t_B$ undergoes a change in its value of y from y_{IV} to y_{VI}. The altered growth curve of this tissue has been plotted as curve VI_B in Figure 4. Now it is possible to determine what the growth rate of a neoplasm will be if the decrease in y occurs early in life, when $t = t_B$, and when $t = t_A$. Looking at Figure 4 makes it apparent that for the same carcinogenic stimulus (the same decrease in y) there is a greater rate of growth of the neoplasm early in life than there is later in life.

In the following we shall use the approximation (18) in carrying out the solution of equations (14), (15), and (16), assuming that F is small. Then it is found that

$$dn/dx = a(F-b)/q - (c+p)T; \tag{55}$$

$$-dF/dx = d - g + fa(F-b)/q - cfT; \tag{56}$$

$$dT/dx = h - m + ia(F-b)/q + (jp - ic)T. \tag{57}$$

It should be noted in this set of equations that when the solution for F becomes greater than $q + b$, we should then apply the set of equations (19) and (20).

Let

$$\begin{gathered} a/q = \alpha, -ab/q = \gamma, -(c+p) = \beta, g - d + afb/q = \phi, \\ cf = \omega, h - m - iab/q = \psi, ia/q = \lambda, jp - ic = \delta, \\ \rho = -\frac{af}{q}. \end{gathered} \tag{58}$$

Then

$$dn/dx = \alpha F + \beta T + \gamma; \tag{59}$$

$$dF/dx = \rho F + \omega T + \phi; \tag{60}$$

$$dT/dx = \lambda F + \delta T + \psi. \tag{61}$$

Solving equations (60) and (61) simultaneously it is found that

$$d^2T/dx^2 + a_1 dT/dx + a_2 T = a_3, \tag{62}$$

where

$$-(\rho + \delta) = a_1, \delta\rho - \lambda\omega = a_2, \lambda\phi - \rho\psi = a_3. \tag{63}$$

The general solution of equation (62) is

$$T = a_3/a_2 + c_1 e^{m_1 x} + c_2 e^{m_2 x}, \tag{64}$$

where

$$m_1 = (-a_1 + \sqrt{a_1^2 - 4a_2})/2,$$

and

$$m_2 = (-a_1 - \sqrt{a_1^2 - 4a_2})/2,$$

and where c_1 and c_2 are integration constants. Solving equation (61) for F and substituting the value of T given in (64) into it we have

$$\begin{aligned} F = &-\delta a_3/\lambda a_2 - \psi/\lambda + e^{m_1 x}(c_1 m_1 - c_1\delta)/\lambda \\ &+ e^{m_2 x}(c_2 m_2 - c_2\delta)/\lambda. \end{aligned} \tag{65}$$

Using equations (64) and (65) in (59) we obtain an expression of the form

$$dn/dx = k_1 + k_2 e^{m_1 x} + k_3 e^{m_2 x}, \tag{66}$$

where k_1, k_2, and k_3 are constant coefficients. Integrating (66) we find that

$$n = k_0 + k_1 x + k_2 e^{m_1 x}/m_1 + k_3 e^{m_2 x}/m_2 \tag{67}$$

with k_0 an integration constant. For the present we defer the study of the properties of equation (71).

V. A. Kostitzin (1939) objects to the use of a single equation to represent growth, holding that the process must be divided into a number of stages, each characterized by its own values of the coefficients in the growth equation used. We have given our coefficients variable magnitudes in a number of cases. The solution of such difficulties is to be accomplished by the use of differential equations in which the coefficients are considered variable. Another possible objection to the present theory is that it does not take into account increase in average cell size leading toward the direction of maturity.

The author is deeply indebted to Dr. Anatol Rapoport for stimulating discussions and guidance in helping him to clarify his ideas on many points; to Dr. I. Opatowski for a critical reading of the manuscript and his helpful suggestions; and also to Professor N. Rashevsky for his continued inspiration.

LITERATURE

Andrew, W. and Cardwell, E. S. 1940. "Neuronophagia in the Human Cerebral Cortex in Senility and in Pathologic Conditions." *Arch. Path.*, 29, 400–414.

Burroughs, E. W., Burroughs, H. S. and Mitchell, H. H. 1940. "The Amino Acids Required for the Complete Replacement of Endogenous Losses in the Adult Rat." *Jour. Nutrition*, 19, 363–384.

Carrel, A. 1931. "Physiological Time." *Science*, 74, 618–621.

Carrel, A. and Ebeling, A. H. 1923. "Antagonistic Growth Principles of Serum and Their Relation to Old Age." *Jour. Exp. Med.*, 38, 419–425.

Child, C. M. 1915. *Senescence and Rejuvenescence.* Chicago: University of Chicago Press.

Cowdry, E. V. 1944. *A Textbook of Histology.* Philadelphia: Lea & Febiger.

Donnan, F. G. 1936. "Integral Analysis and the Phenomena of Life." *Acta Biotheoretica*, 2, 1–11.

Fischer, A. 1946. *Biology of Tissue Cells.* New York: G. E. Stechert & Company.

Heilbrunn, L. V. 1943. *An Outline of General Physiology.* Philadelphia and London: W. B. Saunders Co.

Hinshelwood, C. N. 1946. *The Chemical Kinetics of the Bacterial Cell.* Oxford: The Clarendon Press.

Hogan, A. G. and Pilcher, R. W. 1933. "Effects of Variations in the Amounts of Vitamin B and Protein in the Ration." *Missouri Agricultural Experiment Station Research Bulletin* 195.

Kempner, W. 1936. "Effect of Low Oxygen Tension upon Respiration and Fermentation of Isolated Cells." *Proc. Soc. Exp. Biol. Med.*, 35, 148–151.

Kempner, W. 1937. "Effect of Oxygen Tension on Cellular Metabolism." *Jour. Cell & Comp. Phys.*, **10**, 339–363.

Kesselman, R. H. 1948. "A Mathematical Study of Organism Growth as an Approach to the Cancer Problem." *Bull. Math. Biophysics*, 10, 69–84.

Kostitzin, V. A. 1939. *Mathematical Biology.* London: George S. Harrap & Company.

Little, C. C. 1947. *Genetics, Medicine, and Man.* Ithaca: Cornell University Press.

Lotka, A. J. 1925. *Elements of Physical Biology.* Baltimore: Williams & Wilkins Company.

Moore, R. A. 1944. *A Textbook of Pathology.* Philadelphia and London: W. B. Saunders Co.

Morales, M. F. and Kreutzer, F. L. 1945. "Some Nutritional and Excretional Interactions and the Growth of an Organ or Colony." *Bull. Math. Biophysics*, 7, 15–24.

Muller, H. J. 1947. *Genetics, Medicine, and Man.* Ithaca: Cornell University Press.

Needham, J. 1942. *Biochemistry and Morphogenesis.* Cambridge: The University Press.

Pearl, R. 1927. "The Growth of Populations." *Quart. Rev. Biol.*, 2, 532–548.

Rashevsky, N. 1938. *Mathematical Biophysics.* Chicago: University of Chicago Press.

Rubner, M. 1924. "Die Beziehung des Kolloidalzusstandis der Gewebe für den Ablauf des Wachstums." *Biochem. Ztschr.*, **148**, 187–221.

Schrödinger, E. 1945. *What is Life?* New York: The Macmillan Company.

Smith, P. E. and Copenhaver, W. M. 1948. *Bailey's Textbook of Histology.* Baltimore: Williams & Wilkins Company.

Thompson, D. W. 1942. *On Growth and Form.* New York: The Macmillan Company.

Volterra, V. 1938. "Population Growth, Equilibria, and Extinction under specified Breeding Conditions: A Development and Extension of the Theory of the Logistic Curve." *Human Biol.*, 10, 1–11.

Volterra, V. and D'Ancona, U. 1935. *Les Associations Biologiques au Point de Vue Mathematique.* Paris: Hermann et Cie.

Weiss, S. and Frazier, W. R. 1930. "The Density of the Surface Capillary Bed of the Forearm in Health, in Arterial Hypertension, and in Arteriosclerosis." *Am. Heart Jour.*, 5, 511–518.

Wetzel, N. C. 1944. *Medical Physics* (Edited by Otto Glasser). Chicago: The Year Book Publishers, Inc.

Willis, R. A. 1948. *Pathology of Tumours.* St. Louis: The C. V. Mosby Company.

Wilson, E. B. 1925. *The Cell in Development and Heredity.* New York: The Macmillan Company.

Woodruff, L. L. 1941. *Foundations of Biology.* New York: The Macmillan Company.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 11, 1949

THEORY OF THE MITOTIC INDEX AND ITS APPLICATION TO TISSUE GROWTH MEASUREMENT

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Analysis is made to show that the mitotic index is simply proportional to the ratio of the duration of mitosis (T) to the intermitotic time only under special conditions. In the case of exponential growth of cell population the simple proportionality holds if the product of T and the growth constant is small. For power law (t^n) growth of cell population the simple proportionality holds only when a steady state of growth has existed for at least ten intermitotic periods. The simple proportionality does not apply in conditions of transient growth.

The mitotic index, m/N, for tissues in which mitosis is occurring is defined as the ratio of the number of cells, m, seen in mitosis to the total number of cells, N, examined. The mitotic index has been used to determine the duration in time of the process of division (Hoffman, 1947; Gray, 1931; Laughlin, 1919; Wright, 1925) on the assumption that it is directly proportional to the ratio of the duration of mitosis to the total time between mitoses. In the following analysis we shall show that the direct proportionality holds true only under special conditions.

Designating the mitosis duration as T and the total intermitotic time as L, then $m/N = T/L$ when the value of N is constant with time, i.e., as many cells are being removed as are being produced. Contrasted with this case of the stationary population there are the cases in which the *cell numbers* are known to increase exponentially with time as in transplantable mouse tumors (Hoffman et al, 1943; Reinhard et al, 1945) and in regenerating liver (Brues and Marble, 1937). The purpose of the following analysis is to show how the

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†This document is based on work performed at Los Alamos Scientific Laboratory of the University of California under government contract W-7405-eng-36 and the information contained therein will appear in Division V of the National Nuclear Energy Series (Manhattan Project Technical Section) as part of the contributions of the Los Alamos Laboratory.

mitotic index depends on the parameters of the life cycle (Figure 1) of the cell and on the rate of growth of the cell population. Case I is concerned with the tissue in which exponential growth of cell numbers occurs, while Case II deals with the general case in which the cell number increases as the *n*th power of the time.

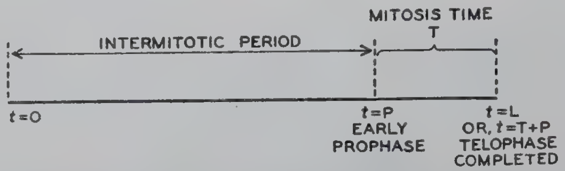

FIGURE 1. Parameters in the life cycle of a single cell which undergoes division. The time between the complete formation of daughter cells is L. When T is small, L is approximately equal to P, the intermitotic time.

Case I. *The number of cells in the tissue mass increases exponentially with time.*

Suppose that no cells are removed. Examples of this case are given in Table I. The number of cells present is then $N_0e^{\lambda t}$ where t is the time in days, N_0 the initial number of cells present, and λ is the characteristic exponential constant.

TABLE I

Tissues in which Cell Numbers Increase Exponentially with Time

TYPE OF TISSUE	λ	REFERENCE
Transplantable mouse adenocarcinoma	0.37 days^{-1}	1, 2
Ascite Tumor cells in mice	0.6 "	3
Transplantable mouse tumor	0.7 "	4
Regenerating liver tissue (rats)	1.3 " *	5

*Maximum, initial value of λ.

1. J. G. Hoffman et al, 1943.
2. M. C. Reinhard et al, 1945.
3. H. Lettre, 1943.
4. S. Konsuloff, 1933.
5. A. M. Brues and B. B. Marble, 1937.

Table I shows the order of magnitude of the values of λ as measured by the volume rate of growth. It is assumed that the cell volumes of the tissues concerned are restricted to fixed limits. Therefore, the value of λ applies to the growth of cell numbers as well as of the tissue volume.

The analysis of the mitotic index is carried out as follows: Suppose that the time schedule in the life of a tissue cell is given by Figure 1. The newly formed cell grows for a time, P, then undergoes mitosis for a time, T; the total time between the appearance of the daughter cells being L. At a time, t, let there be N cells present. The number, m, of cells in mitosis has an age between P and $P + T$. All of these cells must have been born at a time between $t—L$ and $t—P$ or $t—L + T$. The rate of births at any time is $2(dN/dt)$ for binary fission. Therefore, the value of m is given by:

$$m = 2N_0\{e^{\lambda(t-L+T)} - e^{(t-L)}\};$$

or (1)

$$m = 2e^{\lambda(t-L)}N_0(e^{\lambda T} - 1).$$

The mitotic index is m/N and thus becomes:

$$m/N = 2e^{-\lambda L}(e^{\lambda T} - 1).$$

But, $e^{-L\lambda} = 1/2$, since L is the number doubling time for the cells. Therefore

$$m/N = (e^{\lambda T} - 1). \quad (2)$$

Since λT is usually small, this can be approximated by

$$m/N = \lambda T, \quad \text{since} \quad e^{\lambda T} = 1 + \lambda T, \quad (3)$$

and if L is the doubling time, the growth constant, λ, is related to L by:

$$\lambda = \ln 2/L,$$

and the mitotic index becomes

$$m/N = 0.693\,T/L. \quad (4)$$

The essential feature in the expressions (3) and (4) is that the index m/N is proportional to the ratio of the mitosis time, T, and the doubling time, L. And in this case, the value of λ is a measure of the volume rate of growth as well as of the rate of production of cell numbers. Equation (2) shows that if λT is large the mitotic index is no longer simply related to the ratio T/L. However, equation (2) permits an estimation of T once m/N and λ are known.

Case II: *The number of cells in the population increases as* t^n.

The analysis of the case is carried out similar to that given in Case I. The number of cells is given by

$$N = N_0(at^n + 1); \quad (5)$$

the doubling time, t_2, is given by $N/N_0 = 2$, or

$$t_2 = \sqrt[n]{1/a} = L \,. \tag{6}$$

The mitotic index for the general case can be shown to be:

$$\frac{m}{N} = \frac{(t - L + T)^n - (t - L)^n}{t^n - (t - L)^n} \,. \tag{7}$$

By expanding both terms of the numerator and the second term of the denominator it is easily seen that for very large values of t we have

$$m/N = aT \,. \tag{8}$$

Discussion.

An outstanding feature in the foregoing discussion of the mitotic index is the ratio T/L. Few data exist concerning the duration of mitosis, T, which is the datum required if the mitotic index is to be used for determining L. Turning to quantitative data on exponential growth of a tissue mass we shall estimate the duration of mitosis, T, for the Ascite tumor cells in mice from the mitosis data as reported by H. Lettre (1943). He gives values of the cell number doubling time, L, as 25.7, 27.7 and 28.8 hours. From his Table I, we find three values of the mitotic index: 1.5, 1.0, and 1.1%. To compute T we shall use the mitotic index or (mi) = 1% and $L = 25.7$ hours; $T = (\mathrm{mi}) \times L/0.693 = .01 \times 25.7/0.693 = 0.4$ hour or 24 min. This is the lowest value of T to be derived from Lettre's data. Lettre estimates that $T = 15$ min. from the rate of build-up of mitoses in the tumor due to colchicine poisoning.

The transplantable mammary adenocarcinoma in mice described by J. G. Hoffman et al (1943) and M. C. Reinhard et al (1945) lends itself to quantitative estimates for the mitosis time on the basis of the mitotic index. The values found (unpublished data) for the index were: (mi) = 0.3 and 0.5%. The growth constant (Hoffman, et al, 1943) was $\lambda = 0.37$ per day. Hence, $T = 0.004/0.37 = 0.0108$ days, or 15.5 minutes, where we have taken 0.4% as the average value of the mitotic index.

A. M. Brues and B. B. Marble (1937) in their study of the exponential growth of regenerating liver estimate an average time duration of mitosis of 49 minutes. On the other hand, in human scalp epidermis, where it is reasonably assumed that growth is not exponential, J. M. Thuringer (1928) estimated the mitosis duration as being from 15 to 30 minutes.

The analyses given in Cases I and II indicate the nature of the variables which may enter into an interpretation of the mitotic index. For example, in early squamous cell carcinoma of the cervix or of epidermis, where the mitotic index averages 4% and is sometimes as high as 10%, it is first necessary to determine the possibility of T being very long (greater than 1 hour). If T is very long then the mitotic index is correspondingly increased and does not necessarily indicate a high rate of growth. Next it is necessary to know if any of the cells in the preparation were near a region in which they could be removed by differentiation into another cell form or by direct lysis. If neither of these possibilities exists it may be assumed that the population was growing exponentially. If there is evidence that cells might be removed by these processes it is necessary to estimate by which power law of the time, t, the cell population is increasing (or indeed decreasing, depending on the tissue region seen). A similar problem in estimating cell removal rates occurs in the use of the mitotic index to measure growth in tissues under hormonal stimulation such as in the proliferation induced by estrogens.

Summary:

1. It is shown that for exponential growth of a cell population the mitotic index is simply proportional to the ratio of the duration time of mitosis to the intermitotic time only when λT is small. For power law (t^n) growth of a cell population the mitotic index is simply proportional to the ratio of the duration time of mitosis to the intermitotic time only when the population has grown for times long compared with the intermitotic time.
2. For exponential growth of tumors the experimental data are used to compute the time duration of mitosis.
3. Special cases in which the mitotic index cannot be applied due to transient conditions of growth stimulation are discussed.

LITERATURE

Brues, A. M., and Marble, B. B. 1937. "An Analysis of Mitosis in Liver Restoration." *Jour. Exp. Med.*, 65, 15–27.

Gray, J. 1931. *A Textbook of Experimental Cytology.* Chapter 12 on Cell Variability, page 307. Cambridge: At the University Press.

Hoffman, J. G., Goltz, H. L., Reinhard, M. C., and Warner, S. G. 1943. "Quantitative Determination of the Growth of Transplantable Mouse Adenocarcinoma." *Cancer Research*, 3, 237–242.

Hoffman, J. G. 1947. "Wright's Hypothesis: Its Relation to Volume Growth and Mitotic Index." *Science*, 106, 343.

Konsuloff, S. 1933. "Die Impftumoren und die Krebserzeugenden Faktoren." *Ztschr. F. Krebsforschung*, 39, 414–416.

Laughlin, H. H. 1919. "Duration of the Several Mitotic Stages in the Dividing Root Tip Cells of the Common Onion." *Carnegie Inst.*, Washington, No. 265.

Lettre, H. 1943. "Zur Teilungsgeschwindigkeit der Zellen des Mause-Ascites-Tumors." *Die Naturwissenschaften,* 39/40, 467–468.

Reinhard, M. C., Goltz, H. L., and Warner, S. G. 1945. "Further Studies on the Quantitative Determination of the Growth of a Transplantable Mouse Adenocarcinoma." *Cancer Research,* 5, 102–106.

Wright, G. P. 1925. "The Relative Duration of the Various Phases of Mitosis in Chick Fibroblasts Cultivated in Vitro." *Jour. Roy. Micro. Soc.*, 1914.

Thuringer, J. M. 1928. "Studies on Cell Division in the Human Epidermis." *Anat. Rec.,* 40, 1–13.

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MATHEMATICAL BIOPHYSICS
VOLUME 11, 1949

BOOK REVIEW

NORBERT WIENER. *Cybernetics or Control and Communication in The Animal and The Machine.* 1948. 194 pp. New York: John Wiley & Sons, Inc. Paris: Hermann et Cie.

Cybernetics is the name coined by Professor Wiener and his friend, Dr. Arturo Rosenblueth, for "the set of problems centering about communication, control and statistical mechanics" (p. 19) and the present "preliminary book" (p. 153) gives the fundamental concepts on which this branch of mathematics is based as well as a brief survey of the fields to which it might be applied.

The introduction of about 30 pages relates in detail how cybernetics grew up. It tells how Wiener, Bigelow and Rosenblueth came to publish their classical paper, of the Princeton meeting of physicists and physiologists, how, then, the Macy Foundation made possible regular meetings in which the Princeton group was enlarged by psychologists, sociologists and anthropologists as well as by neuroanatomists and neurophysiologists. It tells how the author was requested to write the present book, and it hints finally at the sociological consequences when more and more controls will be built by applied cybernetics which are "bound to devalue the human brain at least in its simpler and more routine decisions" (p. 37).

The word "Cybernetics" is derived from the Greek κ ν β ε ρ ν η τ η σ the latin gubernator. The present reviewer regrets the rendering of the Greek "K", the Latin "G" by a "C". He would have preferred another K. Of course, there are cathodes, but a patient suffers from a kyphosis!

The first four chapters of the book explain on 96 pages the theory. It begins easily enough, with a charming quotation from Wilhelm Hey (d. 1554):

> "Weisst Du wieviel Sternlein stehen
> An dem blauen Himmelszelt?
> Weisst Du wieviel Wolken gehen
> Weithin über alle Welt?
> Gott der Herr hat sie gezählet
> Dass ihm auch nicht eines fehlet
> An der ganzen grossen Zahl."

This leads easily to the recognition that the meteorologist deals with a vast number of approximately equal particles, closely coupled together, while the astronomer studies a relatively small number of particles, greatly diverse in size but coupled with one another only in a very loose way. The chapter goes on to discuss the direction of time, evolution, automatons and robots through the ages, all in a simple language which even a biologist can understand.

The steep ascent to the pinnacle of mathematics is undertaken in the next chapters. The second one, starting out from Gibbs' statistical mechanics and Lebesgue's theory of measure shows "how the whole theory of measure-preserving transformation can be reduced to the theory of ergodic transformation." The third chapter defines information on the premise that "information is the recording of a choice between two equally probable simple alternatives." The amount of information can be defined as "the negative logarithm of a quantity which we may consider a probability" and "is essentially a negative entropy" (p. 78). The theory of time series, information and prediction is then developed at some length. The fourth chapter concerns itself with the theory of feed-back mechanisms, their role in control of performance, and the consequences of their breaking down into oscillations.

The rest of the book shows how cybernetics is applicable to biology and sociology. Computing machines and the Nervous System, Gestalt and Universals, psychopathology and, finally, language and society are examined from a cybernetical point of view. Throughout it is stressed that the important problems are not those of energy or of matter but those of order, i.e., of information. "The mechanical brain does not secrete thought as the liver does bile as the earlier materialists claimed, nor does it put it out in the form of energy, as the muscle puts out its activity. Information is information, not matter or energy. No materialism which does not admit this can survive at the present day."

This truth may by now be self-evident to many, if not to all, who actively work on problems concerning the brain, and is implicit in the whole work of Rashevsky and his school as the numerous diagrams of neuronal circuits which they have constructed show. But the tendency to chase "nervous energy," "Sinnesenergie" through the labyrinths of cerebral pathways is perhaps still lingering on among epistemologists and their friends. Wiener's book can be expected to clarify definitely our thoughts.

Space does not permit to discuss the last chapters in detail. There is much food for thought in them, and there are passages with which many readers will disagree. Let them state their objections as clearly as Wiener stated his case, and they will have benefitted by their reading!

Being a neurologist the reviewer is naturally inclined to evaluate the book peering out of his own little corner as it were. He derives some encouragement for his provincialism from his associations with Professor Wiener in the "Macy meetings" from which he carried with him the impression that the author, too, is passionately interested in the brain and its working. The outline of a theoretical neurology is there, but it is still so general as to require undoubtedly much further work before it will give us full insight into neurological problems. Such work has indeed been actively pursued by Wiener and Rosenblueth, and has even partly been published. Control of muscular activity by the brain is evidently achieved in different ways. The control of voluntary movement, which Wiener considers (see, especially p. 113) is achieved by a system of several feed-backs. The control of respiration, on the other hand, which Wyss and his collaborators analyzed so brilliantly is obviously based on frequency filters in the solitary tract. Hence, one may be well advised not to talk too glibly about "feed-backs."

How adequate Wiener's definition of information will prove to be, only the future can tell. To define information as a simple choice between two alternatives should evoke some contradictions from the Gestalt psychologists. How far or when that symbolific function which was emphasized by Craik ("thought models reality") and which is increasingly commanding attention in certain quarters, can be handled by Wiener's theory, is another puzzling question.

It is not the least value of a good book to set the reader thinking beyond the actual contents of its printed pages. The preceding paragraphs intend first of all to show that Wiener did write a good book. In fact, any one who is or should be interested in problems of relations, be they of neurons or of human beings, or of any other units, or in problems of information, linguistic or otherwise, can do no better than to read faithfully not only Wiener but also all the references he gives!

Unfortunately the publisher has done less than justice to the book. There are several misprints which any good proofreader should have caught. Thus on page 69 in formula 2.24 there appears "l.i.m.," while formula 2.25 has correctly "lim." On page 77, line 8 reads "note that is of the form and." Obviously two formulae have dropped out. The lack of an index in a book which touches on so many subjects is also regrettable. But it should be stated in all fairness that the book is printed on quite heavy paper and seems to stand handling very well, hence it can be leafed through time and time again to find a lost fact or name.

To have made Kybernetics (*sic!*) explicit and to have delineated its scope and its methods is Norbert Wiener's great achievement.

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LITERATURE

Craik, K. J. W. 1943. *The Nature of Explanation.* Cambridge: At the University Press.

Wyss, O. A. N. 1943. "La Régulation de l'Activité Respiratoire Motrice." *Jour. Suisse De Medicine,* 73, 961.